Noncanonical Polyketide Cyclization

and

Stereoselective Synthesis of Configurationally Stable Csp^2-Csp^3 Atropisomers

Inauguraldissertation

zur Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel

von

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Basel, 2019

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

auf Antrag von

Prof. Dr. Christof Sparr

Prof. Dr. Thomas R. Ward

Basel, den 17. September 2019

Prof. Dr. Martin Spiess

Dekan

Für meine Familie

”Das Säure-Base-Gleichgewicht ist wie Robin Hood, immer auf der Seite der Schwächeren.”

Dr. Stefan Frey (†2018), mein erster Chemie-Lehrer

I. Acknowledgments

First and foremost, I would like to thank my mentor and "Doktorvater" *Prof. Dr. Christof Sparr* for giving me the opportunity to work on two very exiting projects in his group. Besides the tremendous progress in theoretical and practical organic chemistry, I had the chance to personally profit a lot from his creativity and curiosity allowing me grow to a scientist.

I would like to thank *Prof. Dr. Thomas. R. Ward* for kindly accepting the co-examination of this thesis as well as *Prof. Dr. Marcel Mayor* for chairing the defense.

I owe special thanks to *Dr. Dominik Lotter* for a close friendship since the first day of our studies in Basel. I appreciated your always honest and critical standpoint in the countless discussions about chemistry but also the good times we had together outside of the lab.

I am grateful to *Dr. Dominik Lotter*, *Daniel Joss*, *Felix C. Raps* and *Martina Piras* for your big effort in proof-reading my thesis.

Many thanks to the former and present *Sparr Group members* for the good times we shared together in the lab, during lunch, somewhere up in the mountains on the group trips and at the Christmas dinners. I am especially thankful to *Dr. Vincent C. Fäseke*, *Dr. Xingxing Wu* and *Dr. Rodolphe Beaud* for their fruitful collaboration resulting in two very exciting projects.

I would like like to thank the talented students *Florian Zellweger*, *Flavio Bianchi*, *Marco Zuccarello* and *Guglielmo Risi* for their contributions to the aldol condensation project.

My research would not have been possible without the excellent analytical service we have here in Basel. For their effort, I would like to thank *PD Dr. Daniel Häussinger*, *Dr. Heinz Nadig*, *Dr. Michael Pfeffer*, *Sylvie Mittelheisser, Dr. Markus Neuburger* and *Dr. Alessandro Prescimone*.

Furthermore, I would to thank *Marina Mambelli-Johnson* for caring about all the administrative work, the *Werkstatt-Team* for a great technical support and *Oliver Ilg* for ordering chemicals and running the shop.

Thanks to the great atmosphere created by all *department members*, I had an unforgettable time during my studies at the University of Basel. Thank you for sharing science and gossip at the apéros and Friday-evening beers.

Trotz der Distanz konnten wir seit der Kanti eine enge und für mich unheimlich wichtige Freundschaft bewahren. Vielen Dank für dieses wertvolle Rückgrat in meinem Leben und ich hoffe, dass wir unser jährliches “Buebereisli” noch lange zusammen weiterführen werden: *Ore*, *Peso*, *Andy*, *Beni*, *Michi*, *Domi*, *Omar*, *Claudio* und *David*.

All dies wäre nicht möglich gewesen ohne die immense Unterstützung meiner Eltern *Susi* und *Paul* wie auch meines Bruders *Simon*. Nebst dem finanziellen Support konnte ich jederzeit auf eure Ratschläge und motivierenden Worte in schwierigeren Momenten zählen, dafür bin ich unendlich dankbar.

Ich habe das Glück eine wunderbare Frau an meiner Seite zu haben, mit welcher ich eine unfassbar schöne Zeit ausserhalb des Labors verbringen darf. *Martina*, herzlichen Dank für deine Liebe, deine Unterstützung und deine Geduld in den arbeitsintensiven letzten zwei Monaten.

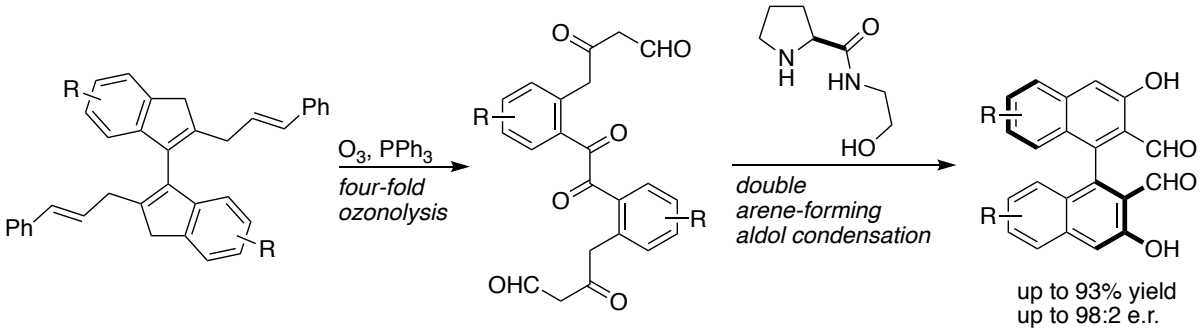
II. Table of Contents

III. Abstract

Noncanonical Polyketide Cyclization

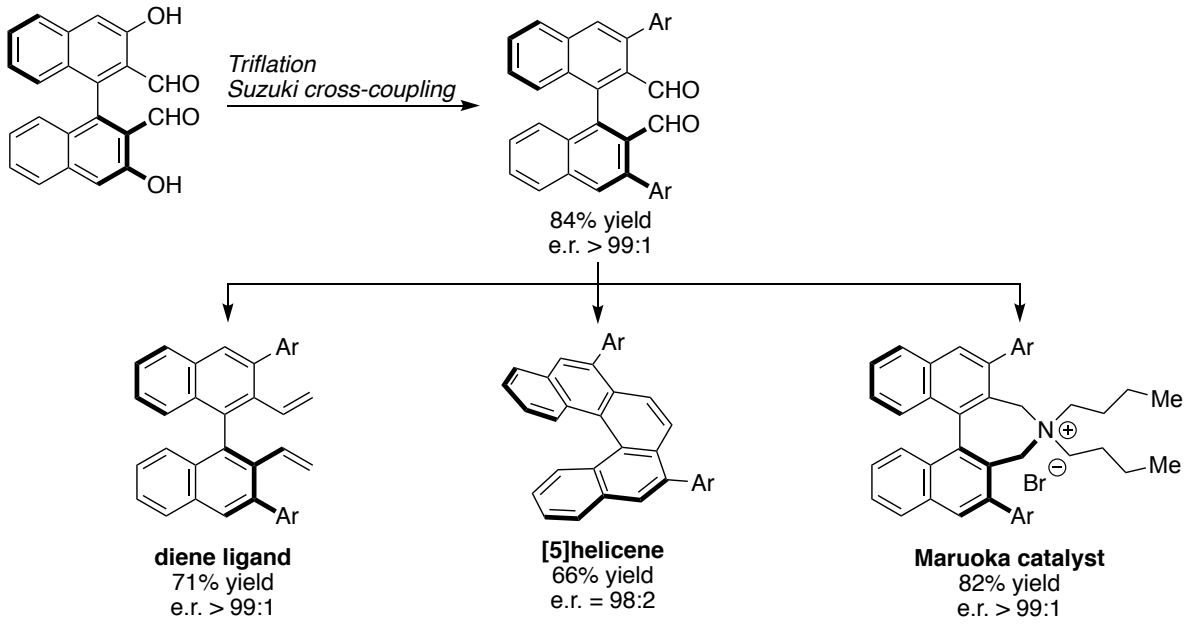
The restricted rotation about a single bond results in stereoisomers that are called atropisomers. Most prominent are biaryl atropisomers, which have emerged to one of the most frequently used scaffolds in stereoselective catalysis. These stereoisomers result from a rotationally restricted Csp^2-Csp^2 single bond that can exhibit substantial configurational stabilities if sufficiently substituted with sterically demanding groups in the *ortho*-position. However, the increased steric demand is often accompanied with difficulties in the preparation and therefore the stereoselective synthesis of biaryl atropisomers still remains challenging.

The arene-forming aldol condensation is a fundamental reaction in the biosynthesis of aromatic polyketides. Strictly controlled by the polyketide synthases, the highly reactive poly-β-carbonyl substrates are diverged into a countless number of aromatic natural products through selective cyclization reactions. Fascinated by the eminent cyclization control, we examined the ability of small-molecule catalysts to selectively convert noncanonical hexa-carbonyl substrates in a double arene-forming aldol condensation culminating in the atroposelective synthesis of tetra-*ortho*-substituted biaryls. The hexa-carbonyl substrates were accessed in a four-fold ozonolysis enabling a late-stage introduction of all carbonyl functions in one step. Secondary amine catalysts capable to form an extended hydrogen-bonding network triggered the noncanonical polyketide cyclization in order to obtain tetra-*ortho*-substituted biaryls in up to 93% yield and with an excellent stereocontrol of up to 98:2 e.r. (Scheme 1).



Scheme 1: The developed four-fold ozonolysis to access noncanonical hexa-carbonyl substrates followed by secondary amine catalyzed the double arene-forming aldol condensation.

The utile hydroxy functions in the 3,3'-position of the binaphthalene product were readily converted into aryl substituents by a triflation and Suzuki cross-coupling reaction. The obtained binaphthalene dicarbaldehyde enabled the straight-forward access to a diene ligand, a [5]helicene as well as the highly valuable Maruoka catalyst in excellent yields. These transformations clearly demonstrated the importance of the established method (Scheme 2).



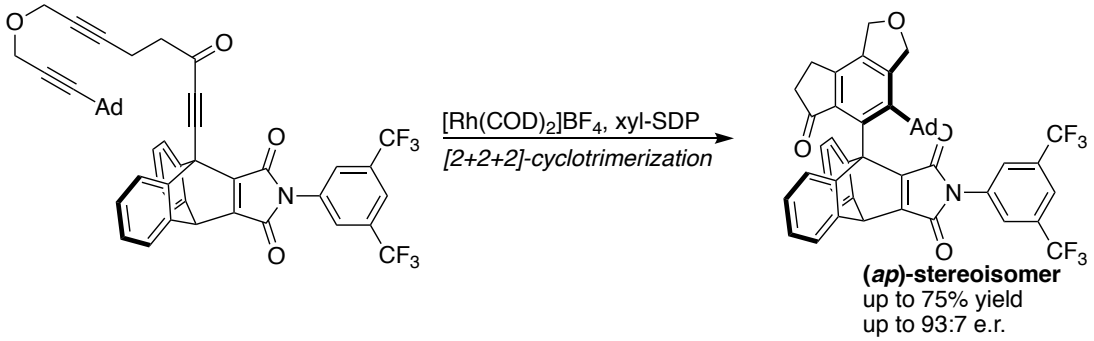
Scheme 2: A diene ligand, a [5]helicene and Maruoka catalyst prepared from the tetra-*ortho*-substituted binaphthalene product obtained in the noncanonical polyketide cyclization.

Stereoselective Synthesis of Csp^2-Csp^3 Atropisomers

Previous stereoselective catalysis aimed at achieving selectivity for one out of two stereoisomers per stereogenic element (2^n). Much less explored, but even more intriguing from a stereochemical perspective, are atropisomers arising from the restricted rotation about Csp^2-Csp^3 axis. In this exciting unprecedented stereochemical scenario, one out of six stereoisomers ($>2^n$) arising from such a rotationally restricted axis is potentially obtained selectively.

To achieve high configurational stability of Csp^2-Csp^3 atropisomers represents a great challenge for the studies of these captivating rotational isomers, and previous investigations of the rotational barrier and isomer-interconversions have been studied after separating racemic mixtures. In this thesis, we intended to contribute to this research field by the development of a [2+2+2]-cyclotrimerization for the first stereoselective synthesis of atropisomers resulting from a rotationally restricted Csp^2-Csp^3 single bond. To suitably evolve stable atropisomeric products, an

adamantyl terminated trialkyne was converted into all three possible diastereoisomers of the Csp^2-Csp^3 atropisomeric product. The low configurational stability of the stereoisomers first prevented their stereoselective preparation, but detailed analysis of the rotational profile enabled to design and synthesize a carbonyl derivative, which provided cyclotrimerization products that exhibit remarkable configuration stability even at temperatures up to 100 °C. A rhodium catalyzed [2+2+2]-cyclotrimerization permitted the first stereoselective synthesis and the reaction was optimized for the (*ap*)-stereoisomer, which could be accessed in good yields of up to 75% and a high enantiomeric ratio of 93:7 e.r. (Scheme 3). In addition to the selective preparation of the (*ap*)-conformer, a second diastereoisomer was synthesized in enantioselectivities of up to 85:15 e.r. as a preliminary result.



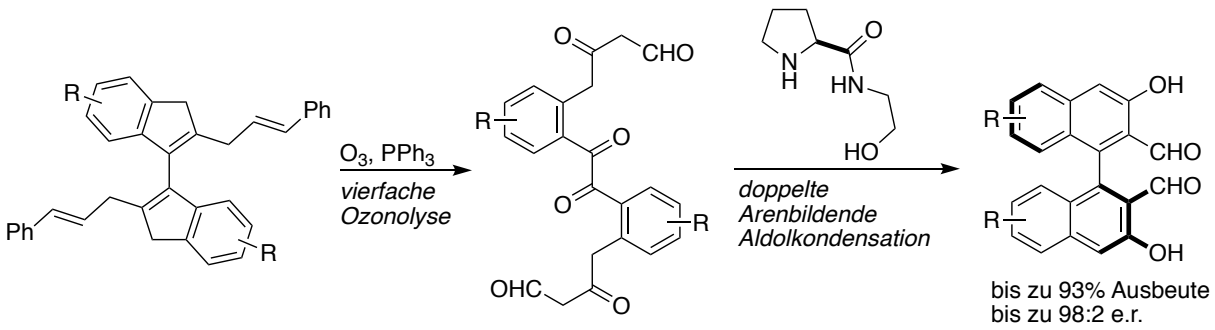
Scheme 3: First stereoselective synthesis of atropisomers resulting from the restricted rotation around a Csp^2-Csp^3 single bond as the only stereogenic element.

IV. Zusammenfassung

Nichtkanonische Polyketide Cyclisierung

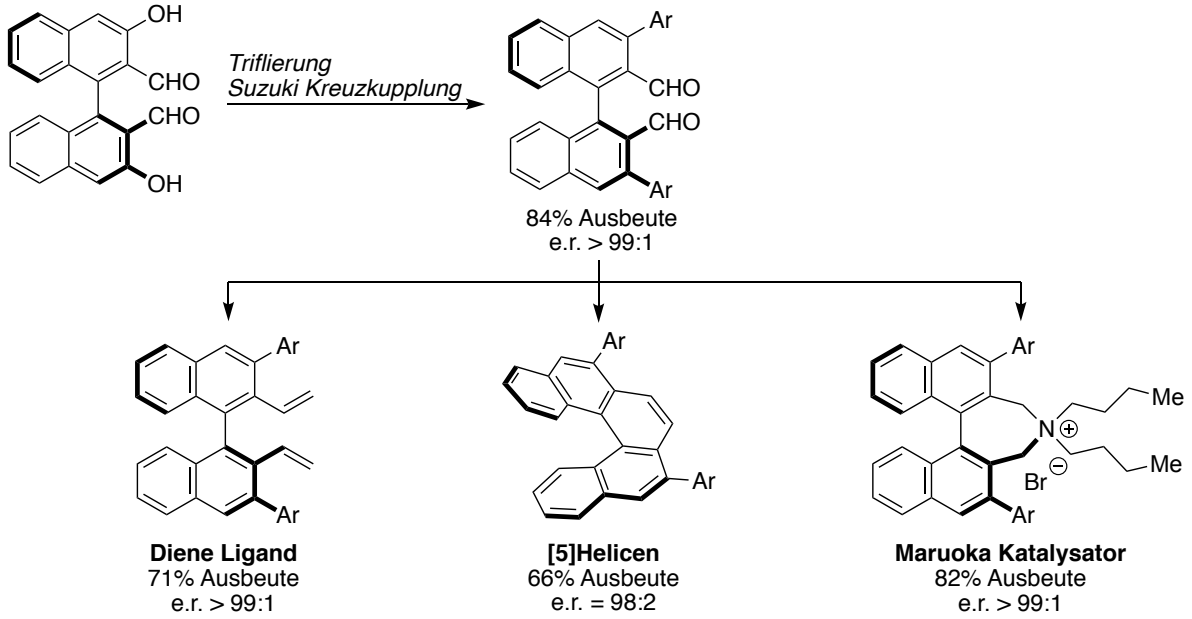
Die gehinderte Rotation um eine Einfachbindung resultiert in Stereoisomeren, welche Atropisomere genannt werden. Biaryle sind die am häufigsten beobachteten Atropisomere und haben sich zu einem der am häufigsten genutzten Grundgerüste der stereoselektiven Katalyse etabliert. Diese Stereoisomere können durch ausreichende Substitution mit sterisch anspruchsvollen Gruppen an den *ortho*-Positionen erhebliche konfigurative Stabilität um die rotationsgehinderte Csp^2-Csp^2 Einfachbindung aufweisen. Der zunehmende sterische Anspruch führt jedoch oft zu Schwierigkeiten in der Herstellung und somit ist die stereoselektive Synthese von Biaryl-atropisomeren bis heute anspruchsvoll.

Die arenbildende Aldolkondensation ist eine fundamentale Transformation in der Biosynthese von aromatischen Polyketiden. Unter strikter Kontrolle von Polyketidsynthasen werden die hochreaktiven Poly-β-carbonyl-substrate durch gezielte Cyclisierungen in unzählige aromatische Polyketidnaturstoffe divergiert. Fasziniert von der überragenden Cyclisierungskontrolle beabsichtigten wir zu untersuchen, ob kleine Molekül-Katalysatoren in der Lage sind nichtkanonische Hexacarbonyl-substrate selektiv in einer doppelten arenbildenden Aldolkondensation zu cyclisieren und damit die atroposelektive Synthese von tetra-*ortho*-substituierten Biarylen ermöglichen. Die Hexacarbonyl-substrate wurden durch eine vierfache Ozonolyse dargestellt, welche die Einführung aller Carbonylgruppen in einen Schritt erlaubte. Sekundäre Amin-Katalysatoren, welche ein erweitertes Wasserstoffbrücken-netzwerk bilden können, bewirkten die nichtkanonischen Polyketidcyclisierung. Dabei konnten tetra-*ortho*-substituierte Biaryle in hoher Ausbeute bis 93% mit hervorragender Stereoselektivität von bis zu 98:2 e.r. hergestellt werden (Scheme 4).



Scheme 4: Die entwickelte vierfache Ozonolyse zu nichtkanonischen Hexacarbonyl-substraten gefolgt von der doppelten arenbildenden Aldolkondensation katalysiert von sekundären Aminen.

Die vorteilhaften Hydroxy-funktionen an den 3,3'-Positionen des Binaphthalenproduktes wurden effizient mittels Triflierung, gefolgt von einer Suzuki-Kreuzkupplung in Aryl-Substituenten derivatisiert. Der dargestellte Binaphthalencarbaldehyde ermöglichte den unmittelbaren Zugang zu einem Dien-ligand, einem [5]Helicen und dem nützlichen Maruoka Katalysator in hoher Ausbeute. Diese Umwandlungen unterstreichen die Wichtigkeit der entwickelten Methode (Scheme 5).



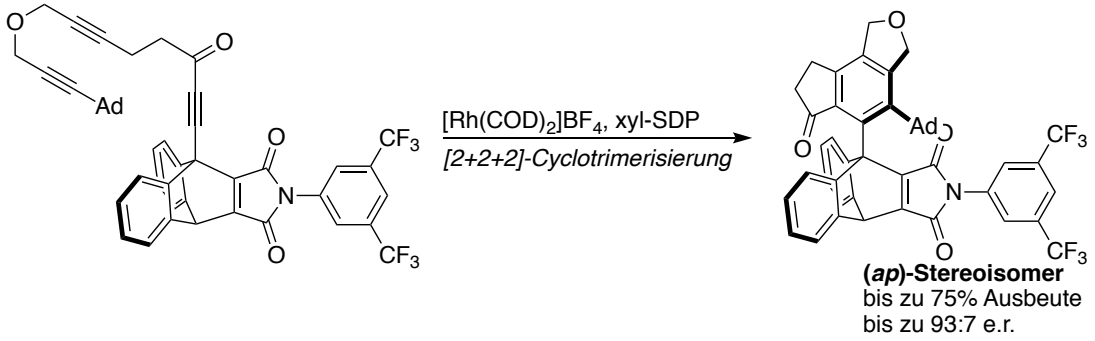
Scheme 5: Die Herstellung eines Dien Liganden, eines [5]Helicen und dem Maruoka Katalysator ausgehend vom tetra-*ortho*-substituierten Binaphthalenprodukt dargestellt durch die nichtkanonische Polyketid Cyclisierung.

Stereoselektive Synthese von Csp^2-Csp^3 Atropisomeren

Bisher befasste sich die stereoselektive Katalyse mit dem Erzielen von Selektivität für eines von zwei Stereoisomeren pro stereogenem Element (2^n). Weniger erforscht, aber umso spannender sind

Atropisomere, welche aus einer rotationsgehinderten Csp^2-Csp^3 Achse resultieren. In diesem spannenden und unbekannten stereochemischen Szenario könnte potenziell Selektivität für eines von sechs möglichen Stereoisomeren durch die Steuerung der Konfiguration der rotationsgehinderten Achsen erzielt werden ($>2^n$).

Das Erlangen von konfigurativer Stabilität von Csp^2-Csp^3 Atropisomeren stellt dabei eine grosse Herausforderung für die Untersuchung dieser Rotationsisomeren dar. Dies erklärt weshalb sich die bisherige Forschung hauptsächlich auf die Bestimmung der Rotationsbarrieren und Isomerumwandlungen nach einer Racematspaltung beschränkte. In dieser Arbeit wollten wir einen Beitrag zu diesem Forschungsgebiet leisten, indem wir mittels einer [2+2+2]-Cyclotrimerisierung die erste stereoselektive Synthese von Atropisomeren, resultierend aus einer rotationsgehinderten Csp^2-Csp^3 Einfachbindung, untersuchen. Die Erforschung von atropisomerischen Produkten mit ausreichender konfigurativer Stabilität resultierte in der Herstellung eines Adamatyl-terminierenden Trialkin, welches in alle drei möglichen Diastereoisomeren des Csp^2-Csp^3 Atropisomerprodukts umgewandelt werden konnte. Die tiefe konfigurative Stabilität der Stereoisomeren verhinderten zunächst deren stereoselektive Herstellung. Eine detaillierte Analyse des Rotationsprofils ermöglichte jedoch die Entwicklung und Synthese eines Carbonylderivates, welches Cyclotrimerisierungenprodukte mit erstaunlich hoher konfigurativer Stabilität bei Temperaturen von bis zu 100 °C hervorbrachte. Eine Rhodium katalysierte [2+2+2]-Cyclotrimerisierung ermöglichte dabei die erste stereoselektive Transformation. In einem ersten Schritt wurde die Reaktion für das (*ap*)-Stereoisomer optimiert, welches in hoher Ausbeute bis zu 75% und guter Selektivität von 93:7 e.r. dargestellt werden konnte (Scheme 6). Zusätzlich konnte ein zweites Stereoisomer in Selektivitäten von 85:15 e.r. zusätzlich zur selektiven Synthese vom (*ap*)-Konformer hergestellt werden



Scheme 6: Erste stereoselektive Synthese von Atropisomeren resultierend von einer rotationsgehinderten Csp^2-Csp^3 Einfachbindung als einziges stereogenes Element.

V. Publications

Parts of this thesis have been published:

- **Catalytic Arene-forming Aldol Condensation: Stereoselective Synthesis of Rotationally Restricted Aromatic Compounds**

  V. C. Fäseke, R. M. Witzig, A. Link, D. Lotter, C. Sparr*, *Chimia*, 2017, *71*, 596–599.

  DOI: 10.2533/chimia.2017.596

- **Stereoselective Arene-Forming Aldol Condensation: Catalyst Controlled Synthesis of Axially Chiral Compounds**

  R. M. Witzig, D. Lotter, V. C. Fäseke, C. Sparr*, *Chem. Eur. J.* **2017**, *23*, 12960–12966.

  DOI: 10.1002/chem.201702471

- **Atroposelective synthesis of tetra-*ortho*-substituted biaryls by catalyst-controlled non-canonical polyketide cyclizations**

  R. M. Witzig, V. C. Fäseke. D. Häussinger, C. Sparr*, *Nat. Catal*. **2019**, *2*, 925–930.

  DOI: 10.1038/s41929-019-0345-0

- **Synthesis of Enantioenriched Tetra-*ortho*-3,3'-Substituted Biaryls by Small-Molecule-Catalyzed Noncanonical Polyketide Cyclizations**

  R. M. Witzig, C. Sparr*, *Synlett* **2019**, *in print*.

VI. Presentations

- "*Atroposelective Double Arene-Forming Aldol Condensation: Synthesis of Tetra-ortho-substituted Binaphthalenes*", R. M. Witzig, V. C. Fäseke, C. Sparr*, Fall Meeting of the Swiss Chemical Society, Bern, 22th August **2017**: poster presentation

- "*Atroposelective Double Arene-Forming Aldol Condensation: Synthesis of Tetra-ortho-substituted Binaphthalenes*", R. M. Witzig, V. C. Fäseke, C. Sparr*, 37th Regio-Symposium, Liestal, 6th–8th September **2017**: oral and poster presentation (awarded with the prize for the best poster)

- "*Atroposelective Double Arene-Forming Aldol Condensation: Synthesis of Tetra-ortho-substituted Binaphthalenes*", R. M. Witzig, V. C. Fäseke, C. Sparr*, Hochschule trifft Industrie, Feldberg-Falkau (DE), 4th–6th October **2017**: oral presentation

- *"Atroposelective Double Arene-Forming Aldol Condensation",* R. M. Witzig, V. C. Fäseke, C. Sparr*, PCC Research Seminar, Basel, 10th April **2018**: oral presentation

- *"Atroposelective Double Arene-Forming Aldol Condensation",* R. M. Witzig, V. C. Fäseke, D. Häussinger, C. Sparr*, 22th ICOS, Florence (IT), 19th September **2018**: poster presentation

- *"Atroposelective Double Arene-Forming Aldol Condensation",* R. M. Witzig, V. C. Fäseke, D. Häussinger, C. Sparr*, 2th Swiss Industrial Chemistry Symposium, Basel 19th October **2018**: poster presentation

- *"Atroposelective Double Arene-Forming Aldol Condensation",* R. M. Witzig, V. C. Fäseke, D. Häussinger, C. Sparr*, 14. Freiburger Symposium, 16th May **2019**: poster presentation

1. Introduction

The concept of symmetry consistently pervades nature so that the appearance of nearly all creatures on our planet including human beings are reflection symmetric, a property that is defined as bilateral symmetric. There are a few well-known exceptions such as flounders or snails having houses, but what is identical for all individuals is the high asymmetry observed on a molecular level. Our life is based on small-molecule building blocks which are chiral, denoting that their spatial arrangement is non-superposable on its mirror image. Thus, DNA strains have a right-handed helical sense of direction due to the configuration of D-2-deoxyribose in the nucleotides and proteins are chiral since they are based on L-amino acids.

The structure of proteins defines the shape of the receptor pockets resulting in different affinities of stereoisomers, which depend on the configuration of the stereogenic elements of the small-molecule antagonists. For example, our nose can differentiate between enantiomers, so that (*R*)-carvone smells like spearmint and (*S*)-carvone displays the typical smell of caraway. This appeared so unrealistic that Miller and his co-worker tediously interconverted one enantiomer into the other in order to unambiguously proof this observation (Figure 1, a).[1] More severe is the potentially different interaction of stereoisomers of active pharmaceutical ingredients possessing stereogenic elements. For example, Ethambutol was discovered as a potent anti-tuberculosis agent and was first sold as a racemate although it contains two stereogenic centers. Severe side-effects of this medication were observed and upon closer examination of the two individual enantiomers. The (*S*,*S*)-form was found being effective against tuberculosis whilst the (*R*,*R*)-form is toxic and responsible for visual impairment. Consequently, the racemic form was withdrawn from the market and today, only the (*S*,*S*)-from is sold, which lowered the toxic optic neuropathy down to approximately 1% (Figure 1, b).[2]

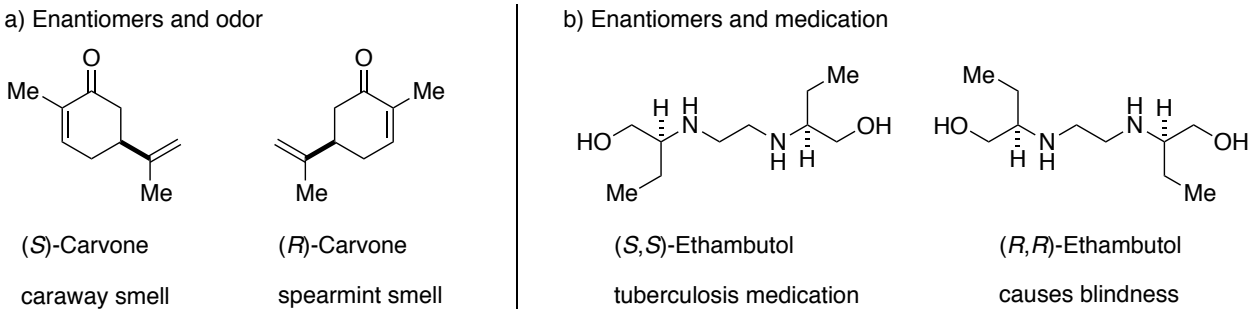


Figure 1: Chiral receptor pockets of proteins result in differentiation of the stereoisomers of small-molecules.

Nature is able to synthesize chiral molecules with excellent selectivity, which includes a diverse set of stereogenic elements as exhibited in the intriguing example of vancomycin (Figure 2). The hepta-peptide derived natural product features one stereogenic axis as well as two stereogenic cycloplanes in addition to numerous stereogenic centers. Vancomycin is used as a last resort antibiotic against multi resistant bacteria strains.[3] Next to the often exceedingly complex architecture of natural products, some contain very unusual characteristics. Two such fascinating molecules were isolated by Isaka and co-workers from an insect pathogenic fungus *Cordyceps nipponica* BBC 1389 during the exploration of potential anti-malarial candidates. The active fraction of the isolation contained four related pyridones. Two of them were stereoisomers resulting from a rotationally restricted Csp^2-Csp^3 single bond, a stereogenic axis which is rarely observed in Nature (Figure 2). [4]

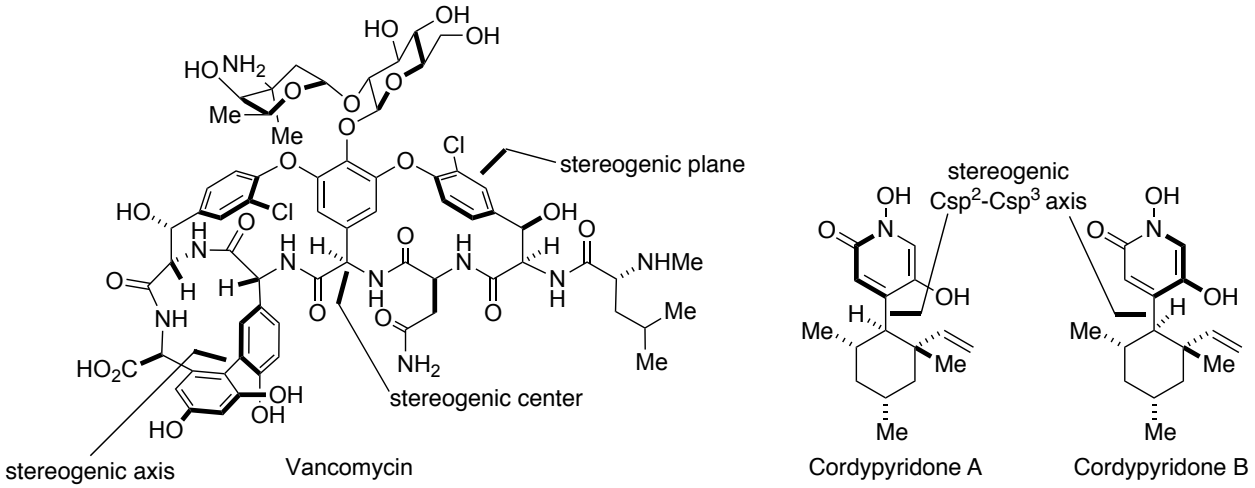


Figure 2: The antibiotic vancomycin containing two stereogenic planes and one stereogenic axis. Cordypyridone A and B are stereoisomers resulting from a stereogenic Csp^2-Csp^3 axis.

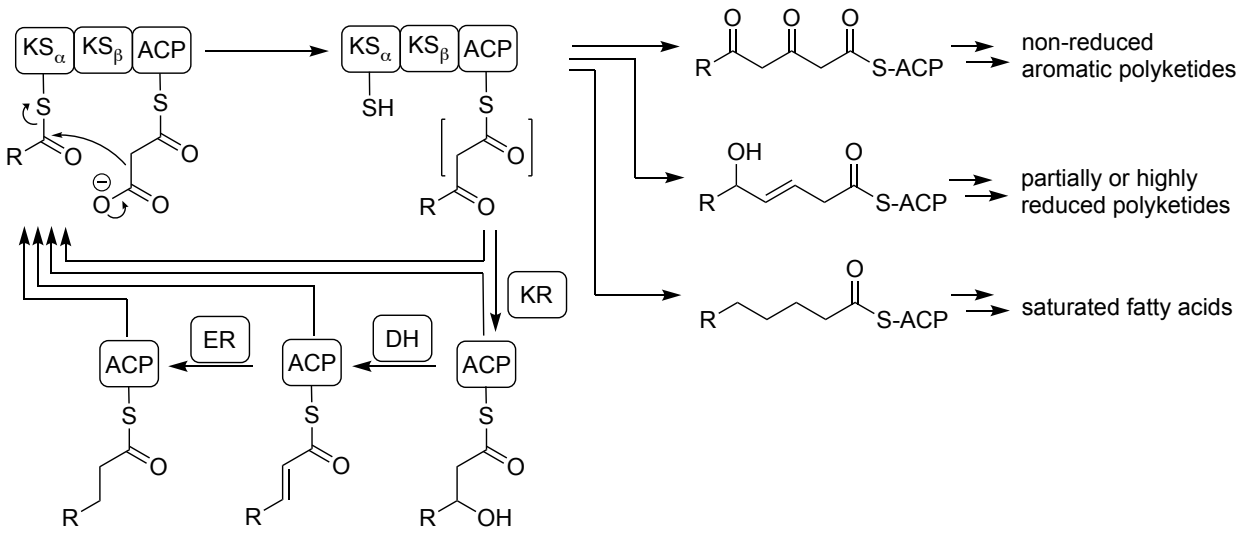
The secret behind the efficient construction of these complex molecular scaffolds and the incomparable selectivity in biosynthesis of natural products are sophisticated enzymes, which are the catalysts used by Nature. Continuously evolved performing one specific transformation, these proteins consist of highly optimized active sites that lead to remarkably selective processes.

1.1. Biosynthesis of Aromatic Polyketides

The exceptional reaction control of enzymes can be well exemplified by the biosynthesis of aromatic polyketides. Precise modifications and selective cyclization reactions induced by enzymatic machineries allow the diversification of precursor molecules to one of the largest families of natural products all originating from simple building blocks. The polyketide biosynthesis can be divided into three stages (chain assembly, cyclization and tailoring steps), whereas divergence is achieved in every phase.[5–7]

1.1.1. Chain Assembly

Polyketide natural products are produced by polyketide synthases (PKS), multifunctional enzymes which have been classified into three different families.[8–9] PKS I contain covalently linked multidomain enzymes while type II and III generally consist of monofunctional enzymes which are dissociable. The synthases of enzymes belonging to class II and III operate in an iterative fashion, thus multiple transformations are performed at one active site. On the other hand, PKS I can be non-iterative and every enzyme domain is catalyzing one specific transformation. The assembly is based on repetitive decarboxylative Claisen type reactions of activated acetate units (for example malonyl CoA) allowing the preparation of poly-β-carbonyl substrates. Thereby, non-reduced poly-β-carbonyl chains are obtained by minimal PKS consisting of two ketosynthases (KS) and an acetyl carrier protein (ACP). After the first diversification obtained through differences in the starting units (Scheme 7, starting group = R), a second distinction is gained by the chain length which is controlled by the two KS in the minimal PKS. Further variation is attained by partial or full reduction of the appended carbonyl function which are optionally obtained through additional ketoreductases (KR), dehydratases (DH) and enoyl reductases (ER). Depending on the degree of reduction, the domains are classified as non-reducing (NR), partially reducing (PR) or highly reducing (HR) (Scheme 7).[7]

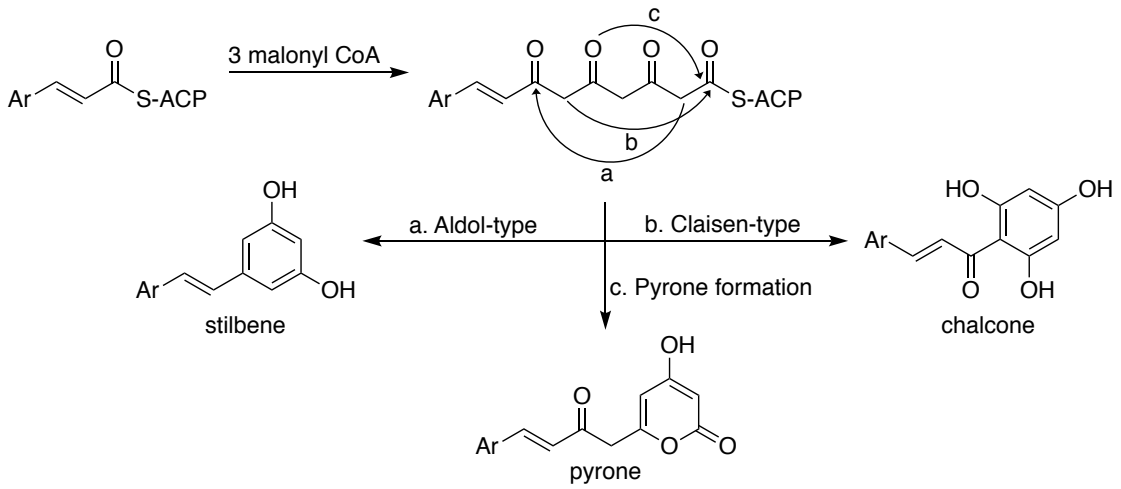


Scheme 7: Diversification of the poly-β-carbonyl substrates based on different starting units, variation of the chain length and partial to full reduction of the appended carbonyl functions.

While a full reduction of the extended carbonyl function leads to a two-carbon extension of the saturated fatty acid chain, the assembly of non-reduced poly-β-carbonyl chain results in highly reactive compounds which can undergo a variety of different cyclizations. Stabilization of the acyclic intermediates is essential, in order to prevent spontaneous cyclizations and to maintain the control over the diversification.

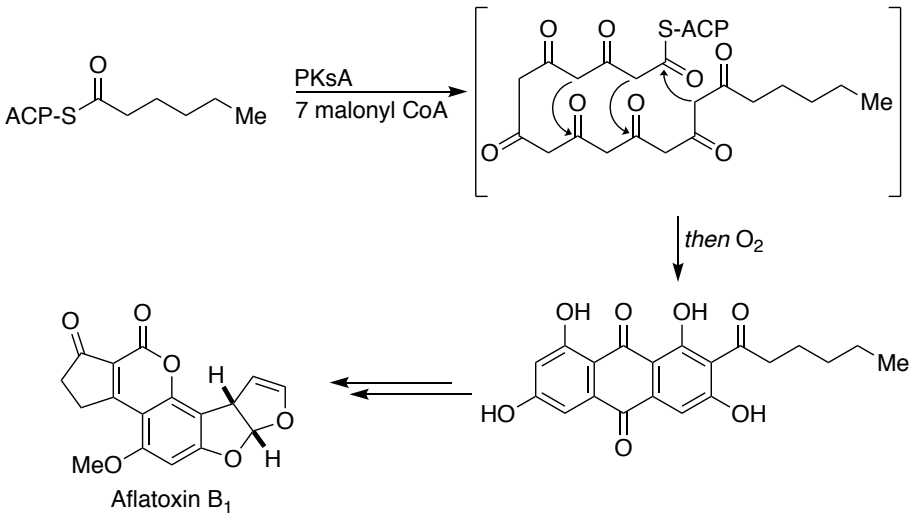
1.1.2. Diversification through Selective Cyclizations

The cyclization of poly-β-carbonyl chains offers an enormous potential for structural variation, which becomes evident by the conversion of an unreduced tetraketide by chalcone synthases. Three different cyclization modes have already been observed from this short poly-β-carbonyl substrate. One aldol-type cyclization is leading to the formation of a stilbene, while the chalcone structure is obtained through a Claisen-type cyclization. A third cyclization possibility is the pyrone formation (Scheme 8).[10] Conceivably, longer substrate chains significantly increase the number of possible cyclizations and therefore increase the need to keep the cyclizations under strict control.



Scheme 8: Three possible cyclizations of an unreduced tetraketide substrate.

Compared to the well explored assembly of the poly-β-carbonyl chain substrates, the detailed operation modes of enzymes to stabilize and selectively cyclize these highly reactive intermediates is less explored. The Townsend group investigated the cyclization of an octaketide to an anthrone intermediate in the biosynthesis of Aflatoxin B_1. Thereby, they deconstructed an iterative multidomain of the polyketide synthase and investigated the individual roles of each domain unit. A product template domain (PT) was discovered, which together with the KS and a thioesterase significantly enhanced the assembly of seven malonyl CoA units and mediated specific cyclizations to the first three rings (Scheme 9).[11]



Scheme 9: Assembly of seven malonyl CoA units and three-fold cyclization followed by an autooxidation to norsolorinic acid in the biosynthesis of Aflatoxin B_1.

The apparent importance of the PT encouraged them to pursue a further exploration of this enzyme domain. The researchers were able to co-crystallize the PT domain with palmitate as an analog for the carbonyl chain substrate and a naphthalene compound as product mimic.[12] The active site of the domain was identified from analysis of the X-ray structure as both co-crystals were located in the same region of the domain. Due to the minimal conformational change between the two crystal structures, which virtually contain the substrate and product of the polyketide cyclization in the active site, they proposed the occurrence of the cyclizations within the detected enzyme pocket. The active site consists of a hydrophilic site to stabilize the carbonyl functions and an opposite hydrophobic site to coordinate the cyclization products. The cyclization chamber in the middle of the pocket suggests a pre-organization of the substrate chain through a "kink" thereby arranging the C4 in close proximity of the proposed catalytic dyad with His^{1345} and Asp^{1543} to undergo a first arene-forming aldol condensation with the ketone C9 (Figure 3, a). The obtained arene is proposed to be further transformed in a similar aldol condensation between the C2 and C11 (Figure 3, b).

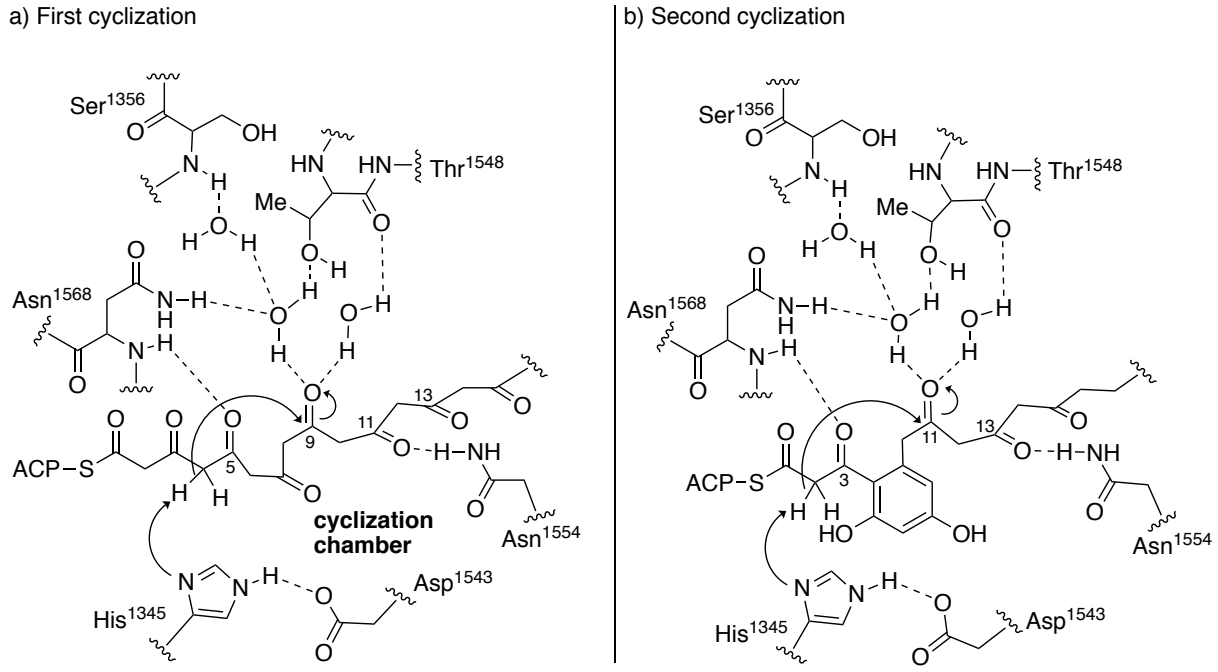
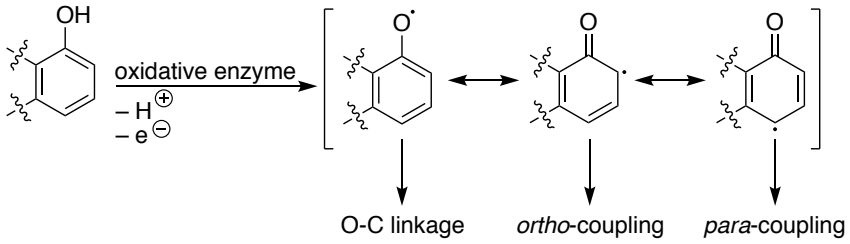


Figure 3: Proposed mechanism for the selective cyclization in the PT domain. The stereogenic centers are omitted for clarity.

Based on the similar domain organization of other non-reducing PKS, the proposed mechanism was hypothesized as being general for non-reducing PKS. The highly optimized enzyme pocket which folds the poly-β-carbonyl substrate for controlled cyclizations indicates the challenge to handle these highly reactive intermediates.

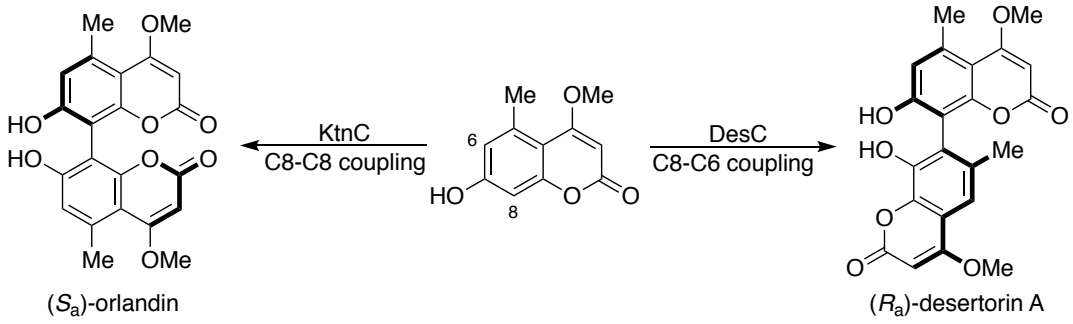
1.1.3. Rotationally Restricted Aromatic Polyketides

Post assembly modifications further extend the diversity of aromatic polyketide natural products. The so-called tailoring steps typically involve glycosylation reactions and various oxidations.[13–14] Particularly interesting are oxidative dimerizations rendering the possibility to form a rotationally restricted axis in diastereoselective[15] or sometimes even enantioselective processes.[16] These radical mediated reactions are catalyzed by oxidative enzymes such as laccases, peroxidases or cytochrome P450 and give rise to a vast variety of dimers due to the stabilization and reactivity of the radical intermediates at the oxygen atom as well as the *ortho*- and *para*-position of the phenol (Scheme 10).[17]



Scheme 10: Stabilized radicals resulting in O-C linkage, *ortho*- or *para*-phenol couplings.

The Müller group explored the responsible gene clusters for the enantioselective dimerization of 7-demethylsiderin and detected a cytochrome gene KtnC being essential for the symmetric *ortho*-phenol coupling to (S_a)-Orlandin, which is an intermediate in the biosynthesis of Kotanin.[18] More recently, they could express the enzymes of KtnC in order to demonstrate that the enantioselectivity observed in the reaction is independent from other enzymes. Furthermore, the *in vivo* expression of the enzyme homologue DesC catalyzed the dimerization to (R_a)-Desertorin A which is a regioisomer of (S_a)-Orlandin, exhibiting the divergence in the biosynthesis of aromatic polyketides in tailoring processes (Scheme 31).[19]



Scheme 11: The oxidative dimerization of 7-demethylsiderin to (S_a)-Orlandin catalyzed by KtnC or to (R_a)-Desertorin using the enzyme homologue DesC.

Until recently, rotationally restricted aromatic polyketides were assumed to be exclusively formed through oxidative coupling processes. However, compared to the regular 1,4 and 1,6 phenol connectivity resulting from oxidative dimerization, the rather unusual pentacyclic fasamycins and related members possess a 1,5 phenol connectivity which suggests an alternative mechanism to form the rotationally restricted axis (Figure 4).[20]

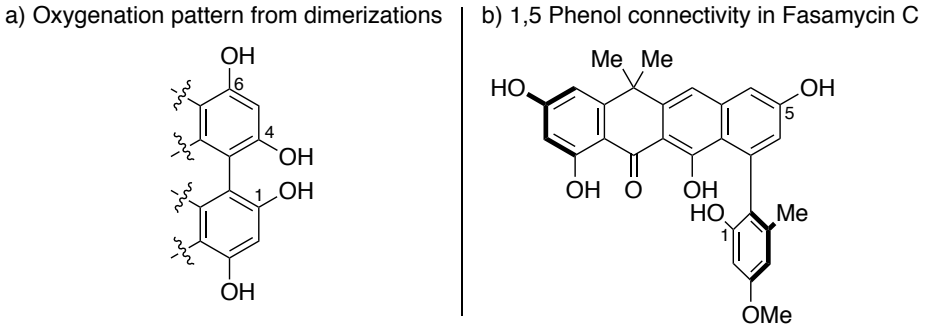
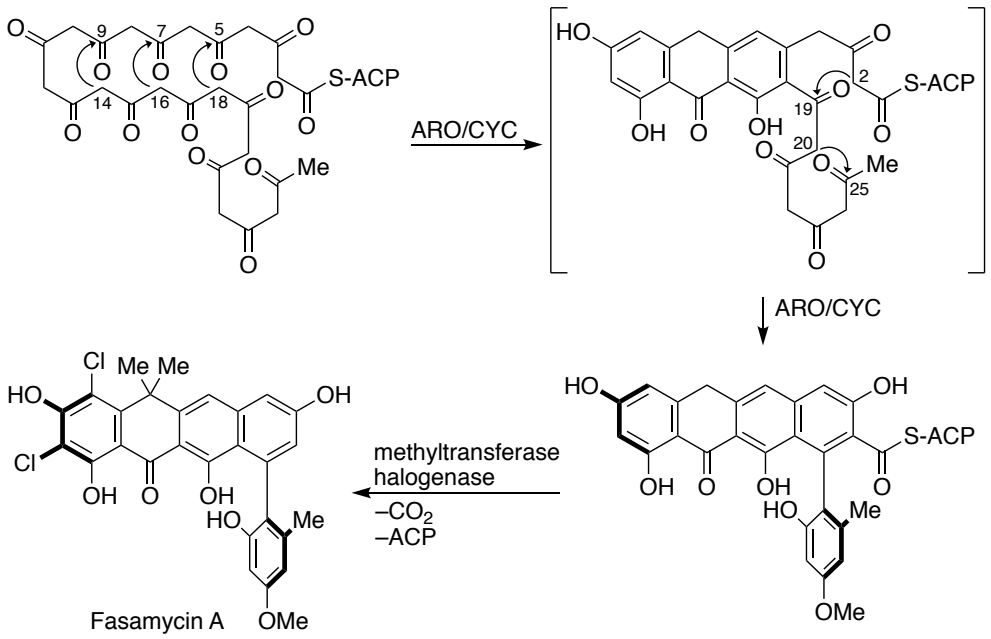


Figure 4: a) Oxidative dimerization resulting in a 1,4 and 1,6 phenol connectivity; b) A 1,5 phenol connectivity in Fasamycin C.

Brady and co-workers proposed that the biosynthetic pathway of Fasamycin A proceeds through the assembly of a non-reduced trideca-ketide by a minimal PKS. Three initial cyclizations (C5 to C18, C7 to C16 and C9 to C14) were proposed being similar to the biosynthesis of γ-Rubromycin, Fredericamycin, Griseorhodin, Benestatin based on the closely related KS genes. Intriguingly, the configuration of the stereogenic axis is defined in the two enzyme-catalyzed cyclizations (C2 to C19 and C20 to C25). Thus, the PKS not only catalyzes a regioselective but even an atroposelective arene-forming aldol condensation.[21] Further tailoring steps such as a decarboxylation, methylation and halogenation finally yield Fasamycin A (Scheme 12).[20]



Scheme 12: Proposed biosynthesis of Fasamycin A by Brady and co-workers.[20–21]

Beyond the impressive divergence in chain assembly, the cyclization processes and tailoring steps of the polyketide biosynthesis, propose biosynthetic pathway of fasamycins highlights the notable control of enzymes by the aldol reaction sequence controlling the configuration of the rotationally restricted axis.

1.2. Atropisomers

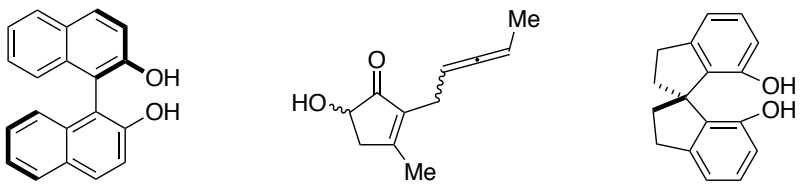
The term atropisomerism originates from the Greek word *atropos* (άτροπος) meaning "without turn" and is used in the context of stereochemistry for a subclass of conformers, which can be isolated into separate chemical species, arising from a restricted rotation about a single bond.[22–23] However, isolation can be broadly interpreted. For most synthetic organic chemists, chemical species are isolated through standard isolation techniques if the compounds are stable at room temperature for hours. In contrast, with modern laboratory infrastructure and fast analytical methods, isolation and detection of molecules in their different conformers can be measured either at very low temperatures or within fractions of seconds.[24] Ōki proposed a practical classification by considering temperature and time factors and suggested that a minimal half-life of racemization of at least 1000 seconds at a given temperature is normally required to isolate an isomer. At room temperature, this would correlate to a rotational barrier of at least 93.3 kJmol^{-1}.[22] This additional

classification provides a suitable first assessment of atropisomers. However, it is defined based on practical aspects of ambient temperature and is arbitrary in view of fundamental properties.

Furthermore, the definition of atropisomers denotes that the rotation as *restricted*, a property that can be seen from different perspectives. The rotation about single bonds was considered being freely rotatable until 1934 when Mizushima and co-workers measured a Raman scattering of 1,2-dichloroethane and carefully analyzed the resulting spectra. The observed four instead of the expected two lines for the C-Cl stretching were only explainable with by existence of rotational isomers.[25] In 1937, based on the work about entropy of gases, Pitzer and co-workers demonstrated that ethane exists longer in the staggered form than in the eclipsed form. Thus, they concluded that a non-uniform rotation is a restricted rotation.[26] Consequently, there are only a few examples with "free rotation" such as the methyl group attached to acetylene.[27] Regardless of the stability of conformers and the half-life of interconversion, a restricted rotation about a Csp^2-Csp^2 single bond gives rise to two enantiomers if *ortho*-substituents are not identical (section 1.3.). If the stereogenic axis possesses at least one tetrahedral carbon (Csp^3), the occurrence of diastereoisomers and enantiomers from only one stereogenic element is possible (section 1.5.). Due to the fact that rotational isomers from a single bond including sp^3 hybridized carbons generally bear a low configurational stability, it is evident that the significantly more stable Csp^2-Csp^2 atropisomers have been discovered first and are commonly described as axially chiral molecules.

"Axial Chirality"

This expression is used to refer to stereoisomerism resulting from a non-planar arrangement of four groups in pairs about an axis of chirality.[23] Biaryls and allenes are the two main classes of molecules belonging to "axially chiral" molecules here exemplified with (R_a)-BINOL and Pyretrolone, the first isolated and characterized natural allene (Figure 5).[28–29] However, it is important to mention that the chirality axis typically refers to an element of symmetry. Thus, the somewhat unrelated spirobiindanes, illustrated as (S_a)-SPINOL, are also often considered being "axially chiral" molecules (Figure 5).[30]



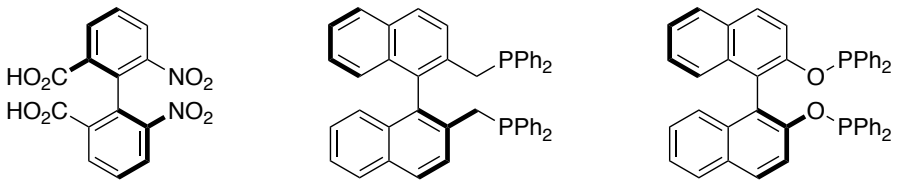
(R_a)-BINOL Pyretrolone (S_a)-SPINOL

Figure 5: Representative examples of "axially chiral" molecules by definition including biaryls, allenes and spirobiindanes.

Additionally, molecules containing a Csp^2-Csp^3 or Csp^3-Csp^3 rotationally restricted axis are, by the previously mentioned definition, not axially chiral since they exceed the defined quantity of four groups in pairs. Furthermore, the term *axial chirality* itself is often misleading, since chirality is an intrinsic geometric feature of the whole molecule,[31] while an axis is a stereogenic element that can lead to stereoisomerism and is only describing the property of one given structural unit of a molecule.[32]

1.3. Csp^2-Csp^2 Atropisomers

The first experimental evidence for atropisomers involved a restricted rotation about a Csp^2-Csp^2 single bond and dates back to 1922 when Christie and Kenner described the resolution of a racemic mixture of *ortho*-substituted biaryl using brucine.[33] The little initial interest in this finding rapidly changed with the discovery of numerous natural products featuring rotationally restricted single bonds. An ever-increasing number of drugs containing a stereogenic axis have been developed.[33–35] Next to atropisomerism in medicinal chemistry, Kumada[36] and Grubbs[37] independently discovered the suitability of rotationally restricted biaryl diphosphines as ligands for transition metal catalysis. However, the selectivity with the new class of phosphine ligand was moderate (Figure 6).



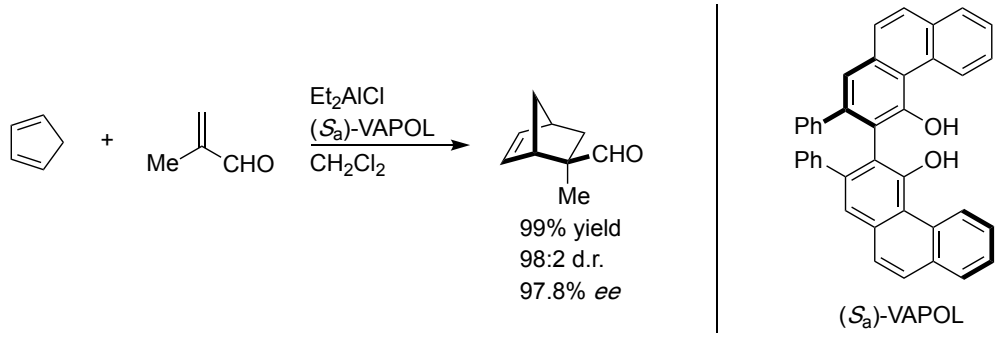
Christie + Kenner 1922 Kumada 1977 Grubbs 1977

Figure 6: Resolved atropisomers by Christie and Kenner and first phosphine ligands based on binaphthalene scaffolds developed by Kumada and Grubbs.

A few years later, Noyori and co-workers developed a new ligand bearing the two phosphines in the *ortho*-position of the binaphthalene scaffold and thus closer to the stereogenic axis when compared to prior ligands. Extraordinary high selectivities were obtained with Noyori's BINAP (2,2'-bis(diphenylphosphino)-l,l'-binaphthyl), setting the basis for a new direction in ligand and catalyst design.[38] From this point, rotationally restricted biaryls have emerged to one of the most important scaffolds in stereoselective catalysis and were considered being a privileged scaffold in enantioselective catalysis.[39] Noyori's groundbreaking work was recognized with the Nobel Prize in Chemistry in 2001 together with Knowles and Sharpless for their contribution in the field of stereoselective catalysis.[40]

1.3.1. 3,3'-Substituted Binaphthalenes in Catalysis

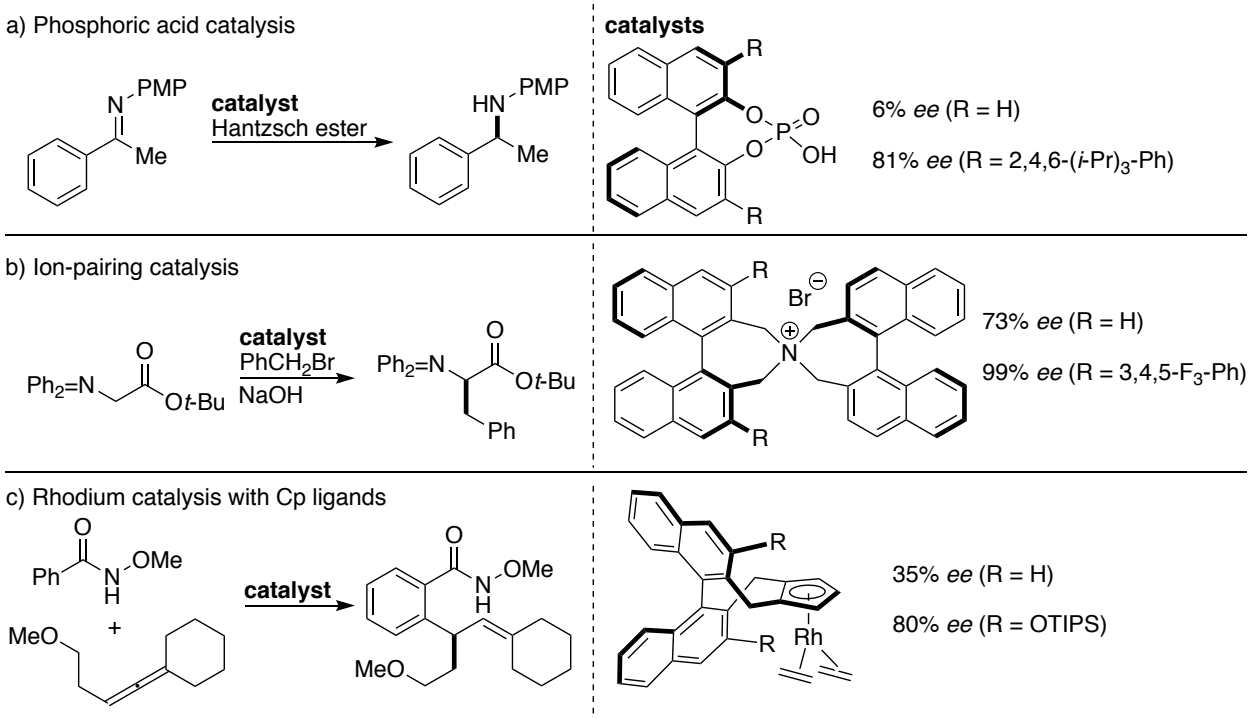
BINAP was found to be an excellent ligand for various transition metal catalyzed reactions.[41] Nevertheless, the development of new ligands continued and novel scaffolds as well as backbone modifications enabled further advances in stereoselective catalysis. Wulff and co-workers recognized that the face discriminating steric bulk in binaphthalene scaffolds is pointing away from the metal center. They thus devised a new ligand bearing the larger residues towards the metal center, ideally with aromatic moieties for a well-defined shielding wall. They synthesized a biphenanthrol ligand (commonly known as VAPOL) which was found to be an excellent ligand for Lewis acid catalyzed Diels-Alder reactions yielding the *exo*-product in quantitative yield with high diastereoselectivities and excellent stereoselectivities (Scheme 13).[42]



Scheme 13: Lewis acid catalyzed Diels-Alder reaction with (S_a)-VAPOL as ligand.

Alternatively to the phenanthrene scaffold, the introduction of substituents in the 3,3'-position of the binaphthalene scaffold was recognized to have a profound positive effect on the stereoselectivity in various catalytic methods. For instance, a low enantiomeric excess of only 6% was observed in an imine reduction catalyzed by a BINOL-derived phosphoric acid, which was

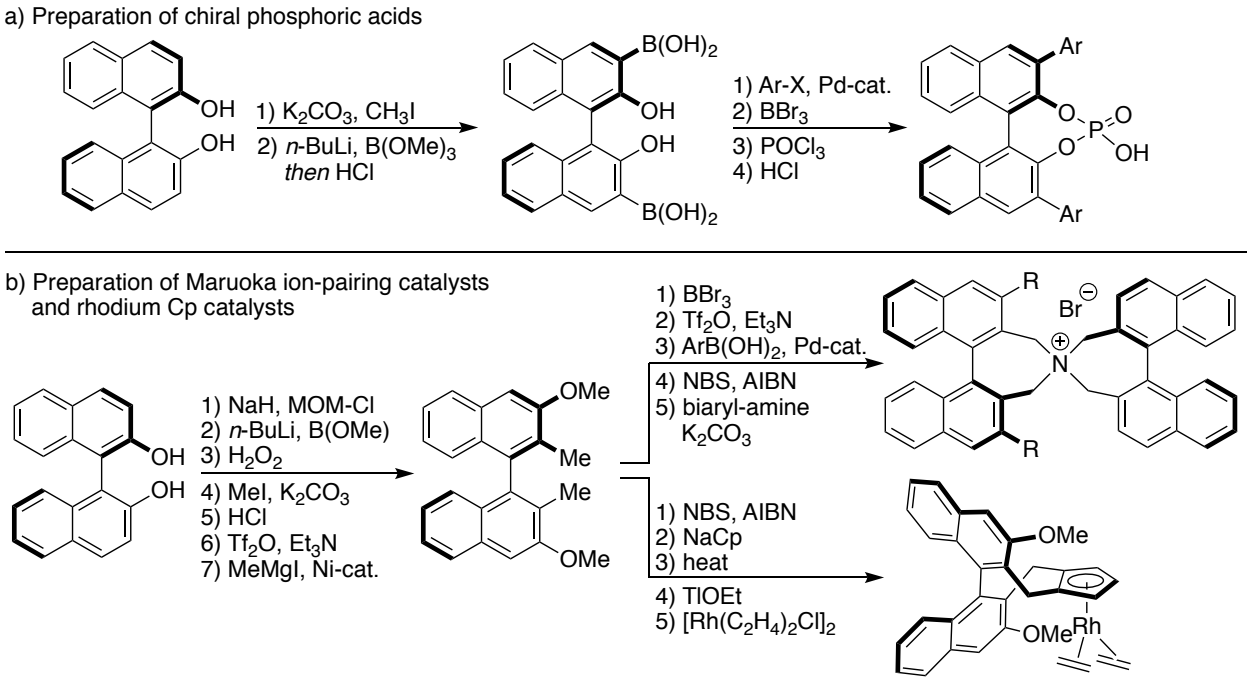
investigated by the List group. Significantly higher selectivities were obtained with phosphoric acids bearing aryl substituents in the 3,3'-position of the binaphthalene core and a major increase to an enantiomeric excess of 81% *ee* was obtained with (*R*)-TRIP containing triisopropyl-equipped aryl substituents (Scheme 14, a).[43] A clear trend was also observed by Maruoka and co-workers by the development of new ion-pairing catalysts. The already suitable enantioselectivity of 73% *ee* observed in the preparation of an α-amino acid with a catalyst based on an unsubstituted binaphthalene core was further increased to an excellent enantiomeric excess of 99% through the introduction of electron deficient aryl groups in the 3,3'-positions of the binaphthalene scaffold of the catalyst (Scheme 14, b).[44] Furthermore, the Cramer group reported a rhodium catalyzed C-H activation with chiral Cp ligands where the stereoselective outcome was again markedly influenced by the 3,3'-substituents. A TIPS protected binaphthol backbone provided the allylated benzamide in 80% *ee* compared to 35% *ee* obtained with an unsubstituted ligand. Further optimization of the conditions allowed to prepare the desired product with up to 93% enantiomeric excess (Scheme 14, c).[45]



Scheme 14: a) Imine reduction with chiral phosphoric acids; b) Ion-pairing catalysis for the preparation of α-amino acid derivatives; c) Rhodium catalyzed C-H activation for the synthesis of allylated benzamides.

Without any doubt, the 3,3'-substituted binaphthalene scaffold has become indispensable for phosphoric acid-,[46] ion-pairing-[47] and transition metal catalysis.[48] However, the considerable

synthetic challenge to introduce substituents in the 3,3'-position of the binaphthalene core is strongly limiting the applicability of these scaffolds. The protection of the hydroxy functions of enantiomerically enriched BINOL followed by a directed *ortho*-lithiation is still a common synthetic strategy, which is siutable for BINOL-derivates for chiral phosphoric acids (Scheme 15, a). [49–50] If additional introduction of carbon atoms in the 2-position is required as for Maruoka's ion-pairing catalyst and the rhodium Cp catalysts, protecting group manipulations render the synthesis relatively laborious (Scheme 15, b).[44–45]



Scheme 15: a) General strategy for the synthesis of 3,3'-substituted BINOL derivates to prepare chiral phosphoric acids; b) Synthesis of Maruoka ion-pairing catalysts and rhodium Cp catalysts starting from BINOL.

More recently, Maruoka and co-workers developed an alternative strategy based on the oxidative dimerization of 2-naphthoic acid to circumvent the additional steps to introduce the carbon in the 2-position of the binaphthalene. This method however requires a resolution and a double directed *ortho*-lithiation is required.[51] A direct stereoselective approach to 3,3'-substituted biaryls, particularly with C-functionalized 2,2'-position would therefore be desirable.

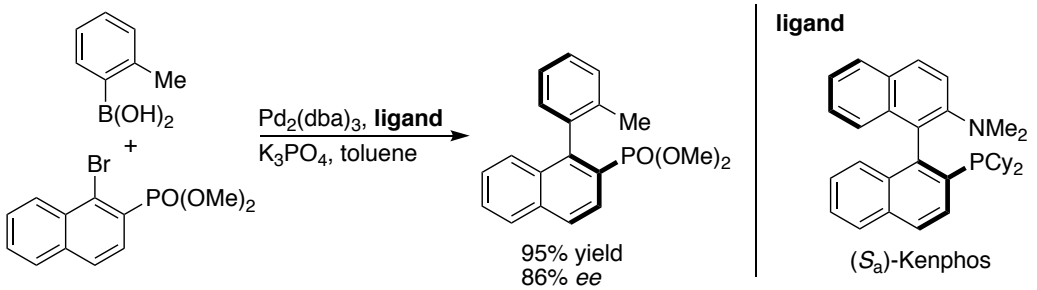
1.4. Stereoselective Synthesis of Csp^2-Csp^2 Atropisomers

The utility of atropisomers in medicinal chemistry and as ligand scaffolds in catalysis encouraged several groups to develop methods for the stereoselective preparation of rotationally restricted

biaryls. The established catalyst-controlled methodologies typically rely on desymmetrization, kinetic resolution, the stereoselective formation of the biaryl bond, the conversion of configurationally unstable biaryls into rotationally restricted compounds and the *de novo* construction of arenes.[52–54] Selected examples are discussed with a focus on biaryl products with potential applications as ligands for stereoselective catalysis.

1.4.1. Atroposelective Cross-coupling Reactions

The substantial steric demand attributed to the *ortho*-substituents intrinsically lowers the reactivity towards the direct formation of the rotationally restricted axis. Thus, besides the template mediated biaryl coupling[55] and diastereoselective Ullmann reactions,[56] enantioselective cross-coupling reactions remain challenging and relatively few methods were reported.[57] Whilst the initially developed Kumada cross-coupling reactions are limited to alkyl substituents,[58] the group of Buchwald described an enantioselective cross-coupling methodology for functionalized biaryls. By a Suzuki cross-coupling strategy for the synthesis of naphthyl phosphonates with high atroposelectivity. The obtained phosphonate was readily converted into a diphenyl phosphine compound as a potential mono-phosphine ligand (Scheme 16).[59]

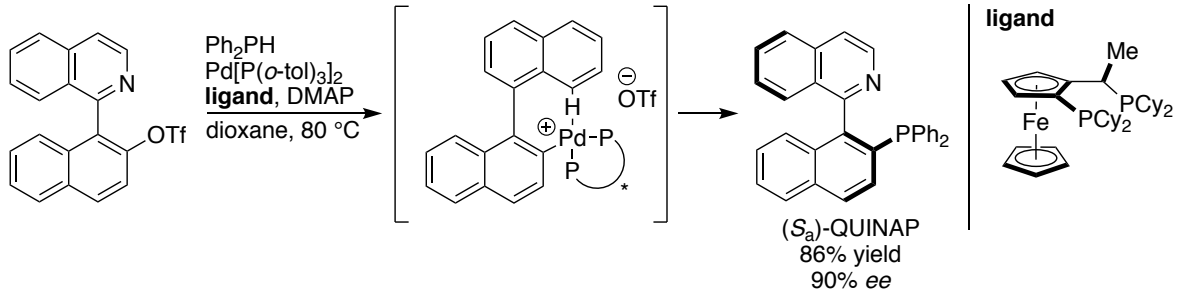


Scheme 16: Atroposelective Suzuki cross-coupling reaction for the preparation of functionalized biaryls.

The preparation of tetra-*ortho*-substituted biaryls resulted in decreased atroposelectivities indicating the challenges for direct formation of such stereogenic axis. Due to these difficulties, atroposelective cross-coupling reactions were complemented with an alternative method, which is inspired by oxidative dimerization of aromatic compounds as observed in the biosynthesis of numerous biaryls natural products.[60]

1.4.2. Conversion of Configurationally labile into Configurationally Stable Biaryls

One strategy to circumvent the tedious formation of the sterically encumbered biaryl bond is to sufficiently substitute a configurationally labile biaryl substrate into a configurationally stable product. The evolved methodologies include the dynamic kinetic resolution (DKR) through the stereoselective introduction of *ortho*-substituents[61] for example by C-H activation strategies.[62] Furthermore, the interconversion of otherwise configurationally stable biaryls was realized through a certain planarization of the biaryl by the formation of a bridging biaryl lactone. The stereoselective lactone opening thereby allowed the atroposelective preparation of various biaryl products.[63] A similar strategy was developed by Stoltz and Virgil for the stereoselective preparation of QUINAP.[64] The examination of conditions revealed the possibility of a DKR starting from the racemic naphthyl triflate, which provided the (S_a)-QUINAP in 85% yield and an enantiomeric excess of 90%. The formation of a square planar palladium complex with an agostic C-H interaction was proposed to enable the rotation about the otherwise stable biaryl axis (Scheme 17).

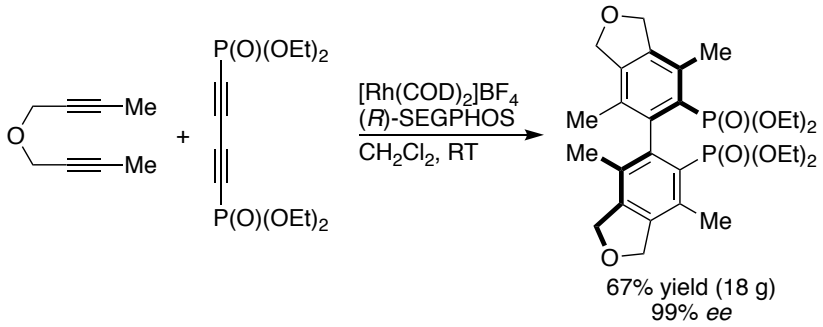


Scheme 17: Palladium catalyzed DKR for the stereoselective preparation of (S_a)-QUINAP.

1.4.3. Atroposelective Synthesis by the *de novo* Construction of Arenes

Controlling the configuration of the stereogenic elements by the formation of arenes emerged as a valuable strategy in the field of stereoselective catalysis.[65] To prepare molecules containing a stereogenic axis, the [2+2+2]-cyclotrimerization of alkyne substrates is particularly versatile strategy, which has been successfully applied for the stereoselective preparation of multi-axis systems, heterocyclic biaryls and axially chiral aromatic amides.[66] Highly substituted biaryls are accessible by the [2+2+2]-cyclotrimerization as demonstrated by Tanaka and co-workers with the synthesis of biaryl diphosphonates as a potential precursor for a novel diphosphine ligand. The

highly active rhodium catalyst allowed to scale up the reaction, which was completed within one hour yielding 18 g (67% yield) of the rotationally restricted compound in an excellent enantiomeric excess of 99% (Scheme 18).



Scheme 18: Rhodium catalyzed [2+2+2]-cyclotrimerization for the stereoselective preparation of biaryl diphosphonates.

Our group contributed to this field of atroposelective synthesis with the development of an arene-forming aldol condensation, which was inspired by the biosynthesis of aromatic polyketides.[67–68] The amine catalyzed aldol methodology was broadly applicable permitting the preparation of binaphthalene carbaldehydes,[69] configurationally stable oligo-1,2-naphthylenes[70], axially chiral amides in high selectivities[71] and even a stereodivergent synthesis of atropisomeric multi-axis systems.[72] The established concept for the *de novo* construction of arenes based on the aldol condensation reaction is more detailed discussed in section 3.1.

1.5. Csp^3-Csp^3 and Csp^2-Csp^3 Atropisomers

Atropisomers resulting from a restricted rotation about a single bond containing at least one tetrahedral carbon (Csp^3) significantly differ from Csp^2-Csp^2 atropisomers. Biaryl atropisomers can exhibit substantial configurational stability and result in two stereoisomers per stereogenic axis similar to stereogenic centers and stereogenic cycloplanes (2^n). On the other hand, generally much lower barriers to rotation are observed for Csp^3-Csp^3 and Csp^2-Csp^3 atropisomers, but in this exciting scenario for stereoisomerism, more than two stereoisomers can result from one stereogenic element (>2^n). The striking number of six stereoisomers is potentially achievable from a rotationally restricted Csp^2-Csp^3 single bond. Consequently, the stereodescriptors R_a and S_a applied for a restricted rotation about Csp^2-Csp^2 single bond are insufficient and an alternative nomenclature has to be used.

1.5.1. Nomenclature

Torsion angles descriptors are ideal to assign rotational isomers resulting from a restricted rotation about a single bond involving tetrahedral carbons and are therefore applied for the nomenclature of the Csp^3-Csp^3 and Csp^2-Csp^3 atropisomers. The torsion angle is defined between the two substituents of highest priority (Figure 7 a: black circle and white oval) as observed in a Newman projection along the restricted axis. The stereochemical arrangements between 0° and ±90° are defined as *syn* and those ranging from ±90° to 180° as *anti*. Additionally, the torsion angles between 30° to 150° and –30° to –150° are called *clinal* while those between 0° and ±30° as well as ±150° to 180° are called *periplanar*. The combination of these terms defines four ranges of torsion angels: *synperiplanar sp* (0 to ±30°), *synclinal sc* (30° to 90° and –30 to –90°), *anticlinal ac* (90° to 150° and –90 to –150°) and *antiperiplanar ap* (±150° to 180°). The torsion angle is considered being positive if the rotation from the top substituent to the bottom one is clockwise through less then 180°, while a negative descriptor requires the rotation in the opposite sense (Figure 7, a).[23]

Three favorable stereoisomers result from the restricted rotation about Csp^3-Csp^3 single bond. If both tetrahedral carbons contain two equal substituents while one is different, a *meso*-isomer is obtained which has the *antiperiplanar* conformation (*ap*). Additionally, the restricted rotation provides a pair of enantiomers in the *synclinal* conformation (*–sc* and *+sc*). This conformation can also be referred as *gauche* conformation (Figure 7, b).

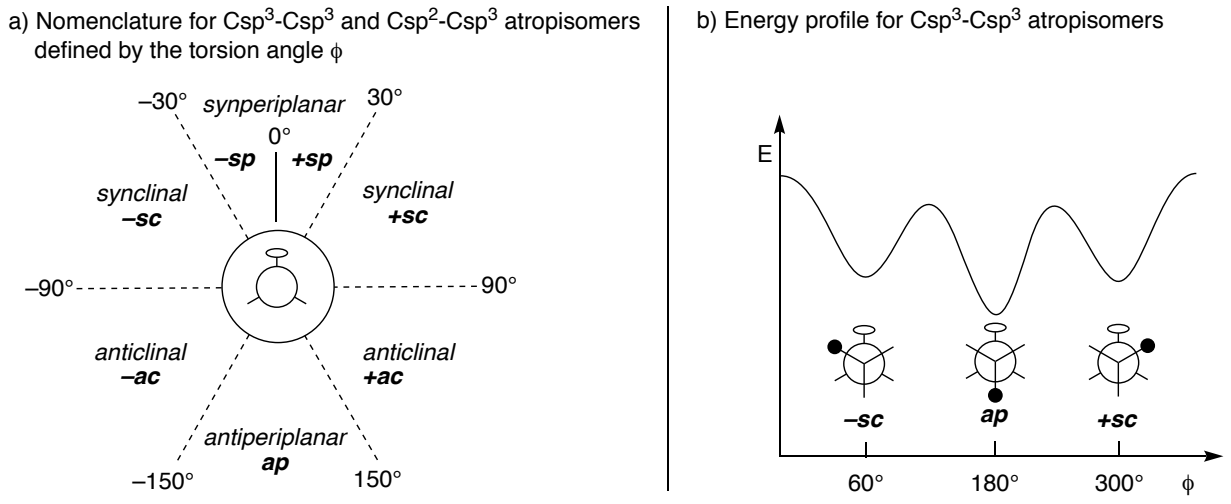


Figure 7: a) Nomenclature for Csp^3-Csp^3 and Csp^2-Csp^3 atropisomers; b) Qualitative energy profile for a Csp^3-Csp^3 atropisomer.

This exceptional situation of enantiomers and diastereoisomers arising from only one stereogenic element is even more illustrative in the restricted rotation about a Csp^2-Csp^3 single bond. Since the two substituents of the sp^2-hybridized carbon are arranged in a planar fashion, a staggered conformation of the (*ap*)-isomer like in the Csp^3-Csp^3 atropisomers is no longer stable. Consequently, the *meso*-form of the *antiperiplanar* isomers would have a highly destabilized eclipsed conformation and therefore emerge as a pair of enantiomers (+*ap* and –*ap*). In contrast to the Csp^3-Csp^3 atropisomers, the *synperiplanar* conformation is at an energetic minimum also existing as two enantiomers (+*sp* and –*sp)*. The *synclinal* arrangement is also expected to be a stable conformation existing as two enantiomers (+*sc* and –*sc*) while the *anticlinal* conformation is likely to be instable similar to the situation in the Csp^3-Csp^3 atropisomers. Thus, the intriguing number of six stereoisomers (three enantiomeric pairs of diastereoisomers) arising from only one stereogenic element is expected (Figure 8).

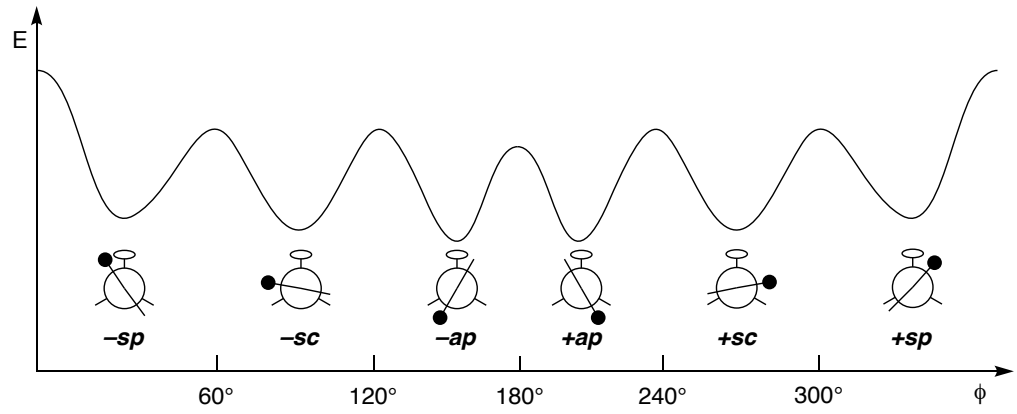


Figure 8: Qualitative energy profile of Csp^2-Csp^3 atropisomers.

Rotational isomers fascinated a small community of scientists that intensively explored the influence of electronic and steric properties on the rotational barrier starting from the 1970's until the late 1990's. At that time, the analysis of enantiomers was more challenging than today and therefore the interconversion of stereoisomers was mostly focused on diastereoisomers rather than enantiomers. 9-Aryl fluorene and triptycene based molecules are the most frequently explored structures among Csp^2-Csp^3 and Csp^3-Csp^3 atropisomers.[73]

1.5.2. 9-Aryl fluorenes

The groups of Sheley, Stewart and Kessler almost simultaneously reported unexpectedly high configurational stabilities for 9-aryl fluorenes.[74–76] The rotational barriers were determined by

NMR, revealing an exceptionally high barrier to rotation of 108 kJmol^{-1} for 9-mesityl fluorene. Illustrative for this high rotational barrier was the absence of coalescence of the signals from the diastereotopic methyl groups in *ortho*-position of the mesityl moiety in the NMR even at temperatures of 190 °C (Figure 9).

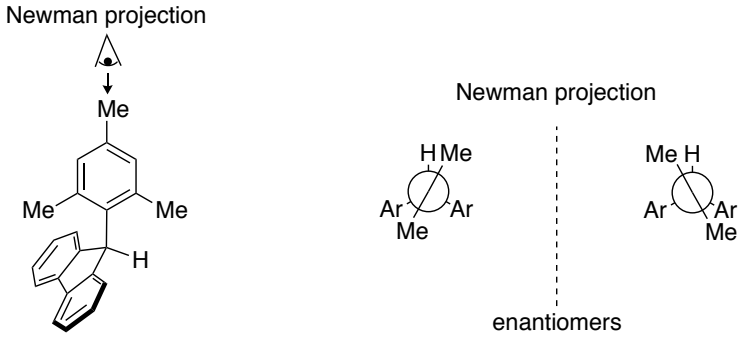


Figure 9: 9-Mesityl fluorene existing as two enantiomers.

The restricted rotation about the Csp^2-Csp^3 single bond of 9-mesityl fluorene results in two enantiomers. To obtain diastereoisomers and enantiomers from such a stereogenic axis, the aryl unit must possess two different *ortho*-substituents if the fluorene is symmetric. Stewart and his co-worker were able to partially separate the (*ap*)- and the (*sp*)-conformers of the 9-(2-methyl naphthyl) fluorene which also exhibited a remarkable configurational stability of 122.2 kJmol^{-1} at 116 °C.[75] Full separation of these isomers was achieved by repeated thin layer chromatography by the group of Ōki, which additionally explored the differences in reactivity of these stereoisomers. The deprotonation of the hydrogen in 9-position of the fluorene was seven times faster at the (*sp*)-conformer when compared to the (*ap*)-isomer, indicating a greater shielding effect by the methyl group than by the arene (Figure 10).[77]

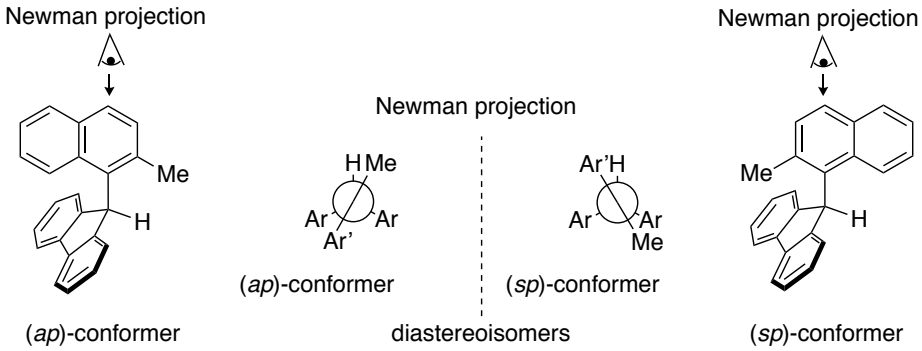
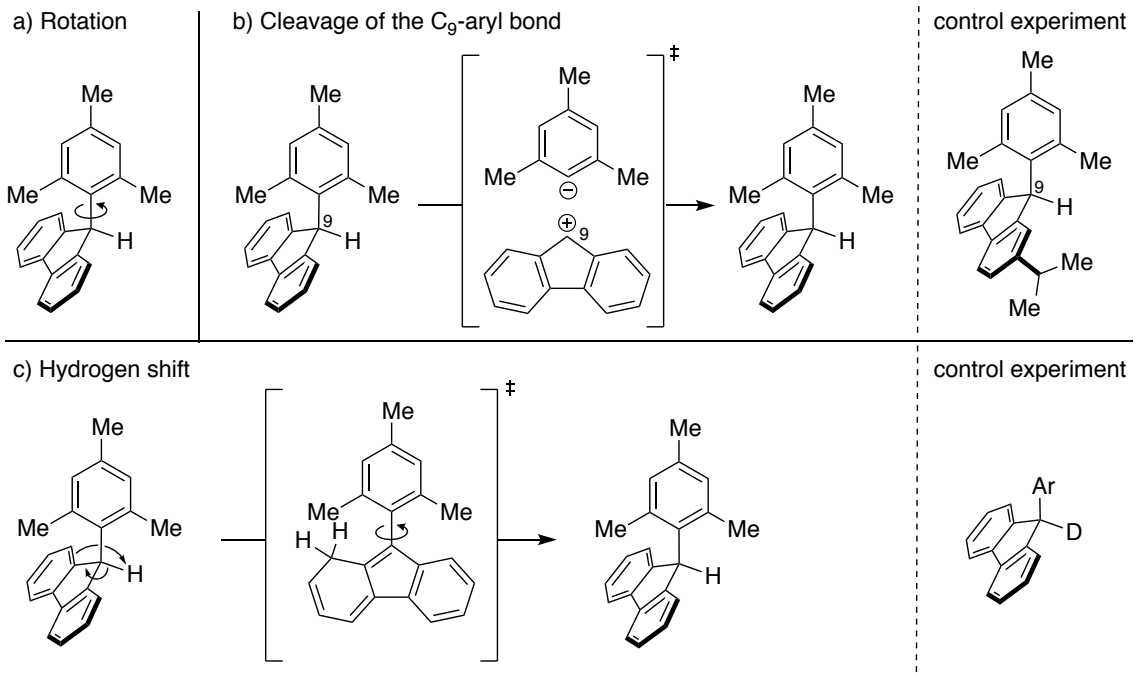


Figure 10: The (*ap*)- and (*sp*)-conformers of 9-(2-methyl naphthyl) fluorene.

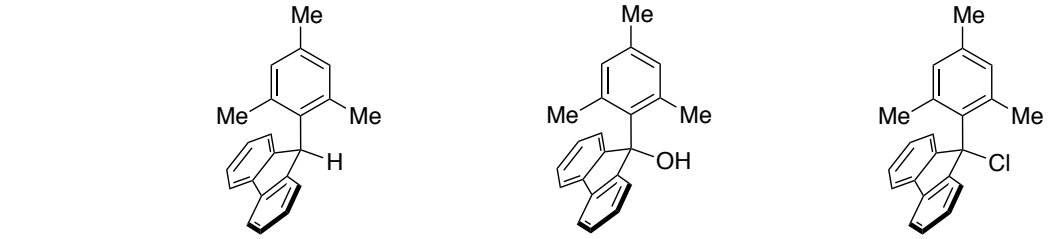
Although rotation about the restricted axis was accepted as a plausible mechanism for the conformer interconversion, a bond breaking event during the isomerization was never completely excluded. The Ford group addressed this possibility and initiated mechanistic investigations concerning the isomerization of 9-aryl fluorenes. Three plausible mechanisms were considered including the rotation about the aryl fluorene bond, cleavage of the rotationally restricted bond and a change in the hybridization state of the tetrahedral carbon through a hydrogen shift. The coalescence of the signals in the NMR at elevated temperatures clearly indicated a rotation about the single bond (Scheme 19, a), but the researcher's aim was wanted to exclude the other possibilities to confirm of their findings. Therefore, they prepared a 2-isopropyl substituted fluorene that was heated until the coalescence was observed. The diastereotopic methyl groups of the isopropyl unit still appeared as two signals. If a bond breaking event would be operational, the two methyl groups would be chemically identical due to the absence of the stereocenter in position 9, thus a bond cleavage was excluded (Scheme 19, b). The incorporation of deuterium in position 9 of the fluorene was used to investigate a possible hydrogen shift during the interconversion. However, the deuterium signal in the NMR spectrum remained unchanged upon heating the compound to 390 °C over 5 hours. As the bond cleavage and a hydrogen shift was excluded as possible interconversion mechanism, the rotation about the restricted axis remained the most plausible interconversion event (Scheme 19, c).[78]



Scheme 19: Plausible interconversion mechanisms considered by Ford and co-workers.[78]

1.5.3. Ground State Destabilization

Even though configurationally stable (*ap*)- and (*sp*)-conformers of 9-aryl fluorenes were isolated, it would be intriguing to explore whether the (*sc*)-conformer, the third possible diastereoisomer, is also accessible. The (*sc*)-conformer was expected to be less stable due to the unavoidable steric interaction of one *ortho*-substituent of the aryl group with one of the arenes of the fluorene. Additionally, the hydrogen atom of the fluorene was expected to provide a very low rotational barrier. Kessler and his co-worker examined whether the rotational barrier is increased if the hydrogen is replaced with more bulky substituents, but they observed exactly the opposite trend. While a configurational stability higher than 104 kJmol^{-1} was observed for the unsubstituted fluorene, a lower barrier to rotation of 84.5 kJmol^{-1} was measured for the hydroxy substituted fluorene and 67.8 kJmol^{-1} for the chlorine substituent. The researchers excluded the formation of a carbocation intermediate since the rotational barrier of the chlorine substituted fluorene is not influenced by the solvent as it would be expected for a cationic transition state and therefore, the isomerization was proposed to proceed through a rotation (Figure 11).[76]



barrier to rotation:	>104 kJmol^{-1}	84.5 kJmol^{-1}	67.8 kJmol^{-1}
(temperature)	>190 °C	145 °C	66 °C

Figure 11: Influence of the substituent in 9-position of the fluorene on the rotational barrier.

The counterintuitive decrease in configurational stability in correlation with the increasing size of the substituent was hypothesized to be caused by a raised ground state energy due to the steric interaction of the substituents. Thus, the transition state energy remains similar but the increased ground state energy of the compound results in a lower rotational barrier, which is the difference between the ground state and the transition state energy (Figure 12).[73] Similar trends were also observed by the groups of Sheley and Rieker.[74,79]

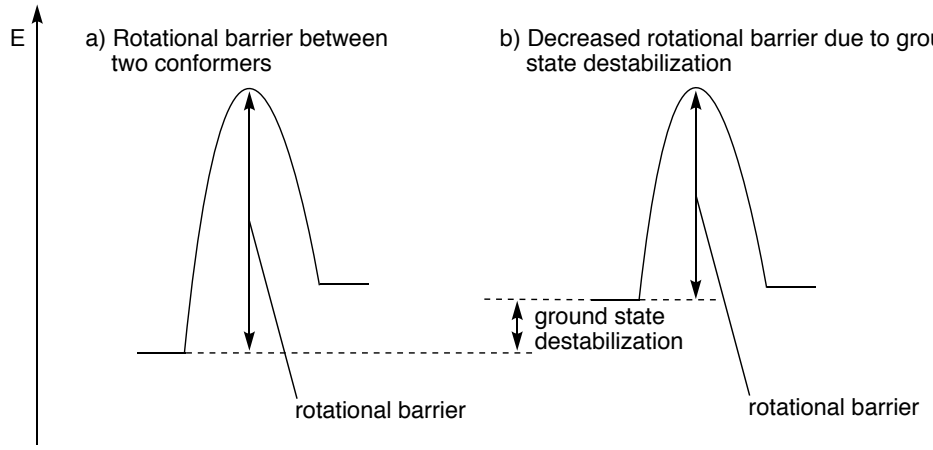
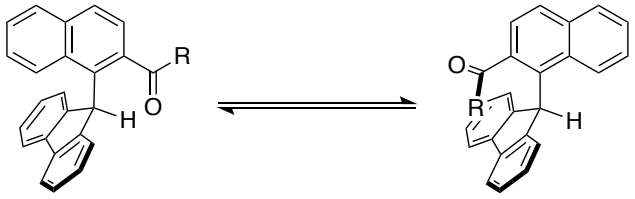


Figure 12: Schematic representation of the influence of the ground state destabilization on the energy difference of the rotational barrier.

The concept of ground state destabilization was further confirmed through the investigation of a series of different carbonyl functions in *ortho*-position of 9-naphthyl fluorenes. The (*ap*)- and the (*sp*)-conformers were isolated and the interconversion barrier was examined in both directions (*ap* to *sp* and *sp* to *ap*). The aldehyde was the only substituent with a comparable barrier to rotation in both directions. For the more sterically demanding carbonyl functions, the rotational barrier was smaller from *ap* to *sp* than the other way around (between 5.4 and 7.9 $kJmol^{-1}$). The energy difference in the rotational barrier was correlated to impossible coplanar arrangement of the carbonyl functions, leading to an increased ground state energy, which thus lowers the barrier to rotation. The similarity of the rotational barriers in both directions for the formyl substrate further supported this notion since a coplanar arrangement of the aldehyde with the naphthalene is feasible and the ground state energies of the (*ap*)- and the (*sp*)-conformers are expected to be comparable (Table 1).[80]

Table 1: Interconversion barriers from (*sp*)- and to (*ap*)-conformers in both directions.



(*sp*)-conformer (*ap*)-conformer

R[a]	**Interconversion**	**$\Delta G^{\ddagger}$ (kJmol^{-1})**
H	*sp* to *ap*	112.5
	ap to *sp*	111.7
CH_3	*sp* to *ap*	111.0
	ap to *sp*	102.9
C_6H_5	*sp* to *ap*	111.3
	ap to *sp*	104.2
OH[b]	*sp* to *ap*	107.5
	ap to *sp*	99.6
OCH_3	*sp* to *ap*	111.3
	ap to *sp*	105.9

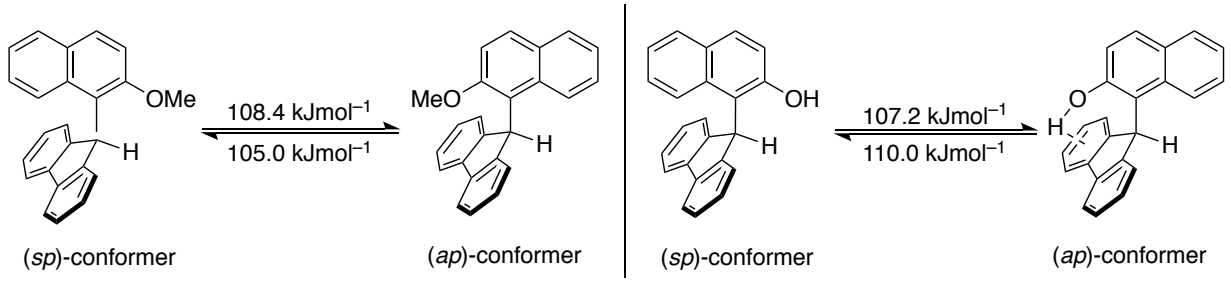
[a] In benzene-d_6 at 55 °C; [b] In DMSO.

If raised ground state energies lead to a decreased barriers to rotation, higher rotational barriers should be obtainable if the ground state energy can be lowered due to stabilization effects.

1.5.4. Ground State Stabilization

In order to investigate the feasibility to increase the rotational barrier through the stabilization of the ground state energy, Ōki and co-worker prepared a series of 9-aryl fluorenes bearing either a hydroxy or a methoxy function in the *ortho*-position of the aryl unit. As both functional groups are approximately equal in size, the steric repulsion would ideally be comparable. However, the hydroxy function was expected to stabilize the ground state energy of the (*ap*)-conformer through a hydrogen bond between the OH and the π-system of the fluorene. A slightly higher rotational barrier from (*sp*) to (*ap*) was measured for the methoxy naphthalene indicating that the (*sp*)-conformer is more stable than the (*ap*)-isomer. With the hydroxy function, a reversed trend was observed where the (*ap*)-conformer had a more stable ground state energy leading to a higher rotational barrier to the (*sp*)-conformer than the other way around. The stabilization of the (*ap*)-

conformer is most likely induced by a hydrogen-bonding interaction between the hydroxy to the π-system of the fluorene as anticipated (Scheme 20).[81]

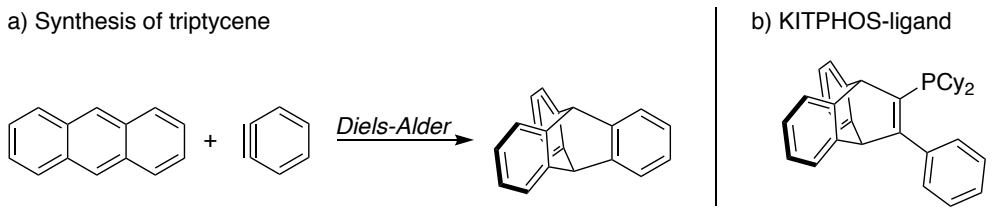


Scheme 20: Ground state stabilization through a hydrogen bond between the OH and the π-system of the fluorene.

The investigations of the restricted rotation about the Csp^2-Csp^3 single bond of fluorene derivates impressively demonstrated the correlation between the barrier to rotation and the ground state energy, which is highly sensitive to steric interactions. Increased ground state energies lead to lower barriers to rotation while a ground state stabilization results in higher rotational barriers. Thus, to obtain configurationally stable Csp^2-Csp^3 atropisomers, a high stabilization of the ground state energy in combination with a high barrier to rotation has to be attained. The fluorene core enabled the preparation of configurationally stable (*ap*)- and (*sp*)-conformers but the observation of the third possible conformer (*synclinal*) was not reported for fluorene compounds. From molecular models, it becomes evident that the (*sc*)-conformer of 9-aryl fluorenes will be highly destabilized. Furthermore, the implementation of an additional rotational barrier through a substituent in the 9-position of the fluorene without severely increasing the ground state energy appears highly challenging. Hence, investigations of rotationally restricted axis including a tetrahedral carbon have also been focused on other structures besides the fluorene and one particularly promising motif was found with triptycene compounds.

1.5.5. Triptycenes and Derivates

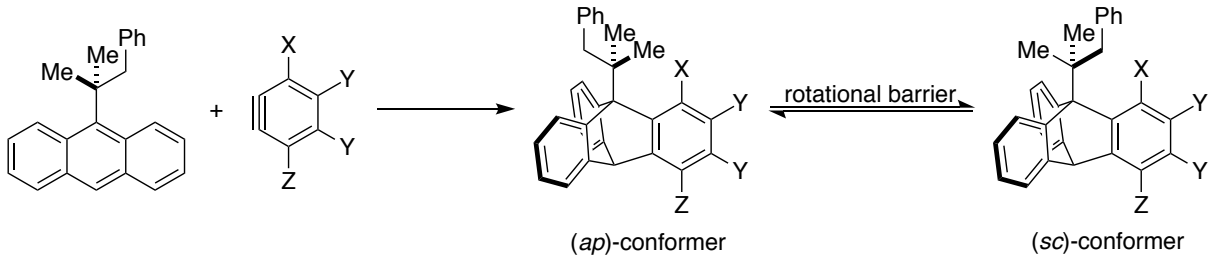
Triptycene belongs to the barrelene type compounds and possesses a trigonal arrangement of three benzene rings forming a rigid scaffold. This structurally interesting molecule is readily accessible from Diels-Alder reactions of anthracene and benzyne (Scheme 21, a).[82] Due to its well-defined structure, it has been utilized as backbone for ligands, which were found being very efficient for C-C and C-N cross-coupling reactions and gold catalysis (Scheme 21, b).[83]



Scheme 21: a) Diels-Alder reaction of anthracene and benzyne for the preparation of triptycene; b) KITPHOS-ligand developed by the group of Hashmi.[83]

Concerning the restricted rotation about the Csp^2-Csp^3 and Csp^3-Csp^3 single bonds, the triptycene unit offers a unique molecular structure providing three well-defined cavities. To obtain distinguishable stereoisomers, one of the three benzene units needs to be substituted in order to desymmetrize the triptycene structure. Molecular models revealed that the distance of the *tert*-alkyl substituent in the 9-position towards the hydrogen in the *peri*-position of the triptycene is only 1.5 Å, which is by far smaller than the sum of the van der Waals radii. Therefore, the introduction of substituents was predicted to have a great influence on the configurational stability. Ōki and co-workers prepared a series of 9-alkyl triptycenes bearing substituents in the *peri*-position through the Diels-Alder reaction between 9-alkyl triptycene and substituted benzynes. The Diels-Alder reaction yielded exclusively the (*ap*)-conformer except for the mono-fluoro substituted triptycene where the (*sc*)-conformer was obtained. With various *peri*-substituted triptycenes in hand, the influence of the substituents on the rotational barrier of the Csp^3-Csp^3 single bond was examined. Exceptionally high configurational stability of 169 $kJmol^{-1}$ was found for the triptycene with no *peri*-substituent. Even higher rotational barriers were determined for small substituents such as fluoride and methoxy. On the other hand, an increase in steric demand was proportional with a decreasing rotational barrier exemplified in the considerably lower configurational stability of 140.4 $kJmol^{-1}$ obtained for the trifluoromethyl substituted triptycene. This trend is in agreement with the previously mentioned theoretical explanation of a lowered rotational barrier through ground state energy destabilization observed in sterically demanding systems (Table 2).[84]

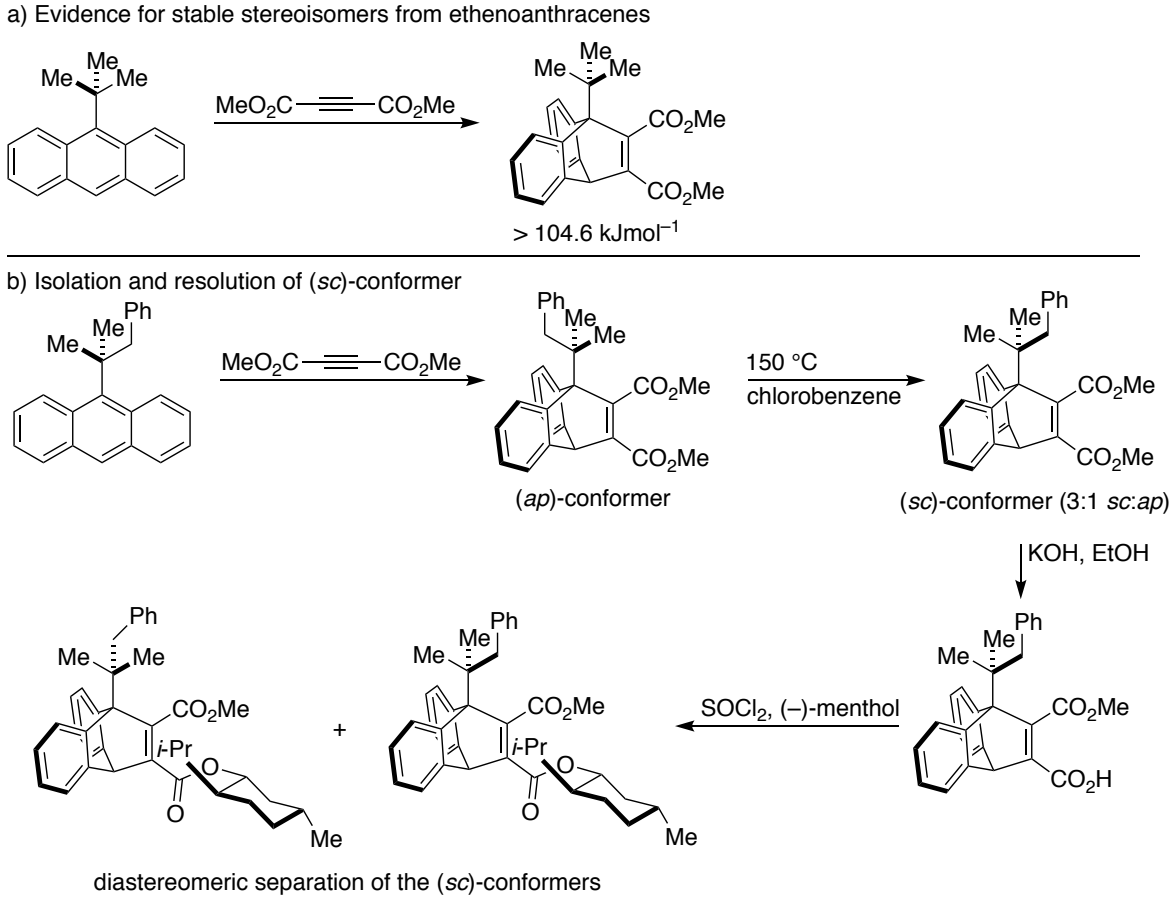
Table 2: Influence of the *peri*-substituents of the triptycene on the rotational barrier.



X	Y	Z	$\Delta G^{\ddagger}$ (kJmol^{-1})
H	Cl	H	169.0
F	H	H	180.7
OCH_3	H	OCH_3	177.8
Cl	H	H	169.0
Br	H	H	164.0
CH_3	H	CH_3	160.7
CF_3	H	H	141.4

Furthermore, the triptycene scaffold has been used to explore the rotational behavior of compounds bearing secondary alkyl substituents[85] and primary alkyl substituents[86] in the 9-position, which generally results in a much lower barrier to rotation compared to the *tert*-alkyl triptycenes. While the steric demand of triptycenes cannot be further decreased through substituents in the *peri*-position of triptycene, related derivates have been examined. Ōki and co-workers found promising evidence to obtain a configurationally stable Csp^3-Csp^3 axis from an ethenoanthracene that was prepared through a Diels-Alder reaction of 9-*tert*-butyl anthracene and dimethyl acetylenedicarboxalate. With the *tert*-butyl substituent in the 9-position, a rotational barrier of 104.6 kJmol^{-1} was estimated, but no stereoisomers result from this structure due to the symmetry of the *tert*-butyl group (Scheme 22, a). Thus, the Diels-Alder reaction was performed with (1,1-dimethyl-2-phenylethane)anthracene and the (*ap*)-conformer was obtained in a yield of 75% determied by NMR together with 15% of the racemic (*sc*)-conformer. Thermal isomerization allowed to enrich the (*sc*)-conformer to a 3:1 ratio compared to the (*ap*)-form and enabled the isolation. Under basic conditions, one ester function of the (*sc*)-conformer was saponified and the subsequent esterification with (–)-menthol allowed the diastereomeric separation of the racemic

(*sc*)-conformer proving the existence of enantiomers resulting from a restricted rotation about a Csp^3-Csp^3 single bond (Scheme 22, b).[87]



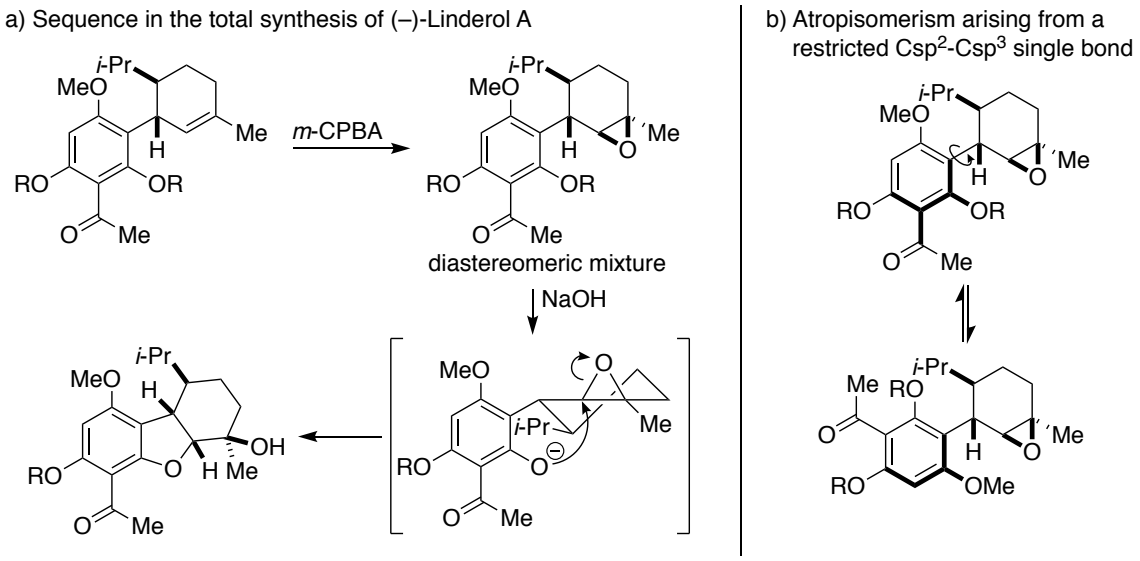
Scheme 22: a) Unexpected high rotational barriers were observed for *tert*-alkyl ethenoanthracene; b) Resolution of configurationally stable (*sc*)-conformers.

Besides the detailed investigations of the conformational preferences of stereoisomers resulting from a rotationally restricted axis involving at least one tetrahedral carbon, the origin of the configurational stability was mostly rationalized through molecular models or the sum of van der Waals radii indicating steric repulsion. Nowadays, more precise identification of essential interactions and stabilization energies is possible with the support of computational analysis.

1.5.6. Rotational Isomer Analysis Supported by Computational Modeling

Berber and co-workers completed a total synthesis of (–)-Linderol which included an intramolecular dihydrofuran formation through the opening of an epoxide. During the preparation of the desired epoxide substrate, they observed the formation of diastereoisomers, which could not be separated by chromatography. Thus, subsequent dihydrofuran formation was investigated with

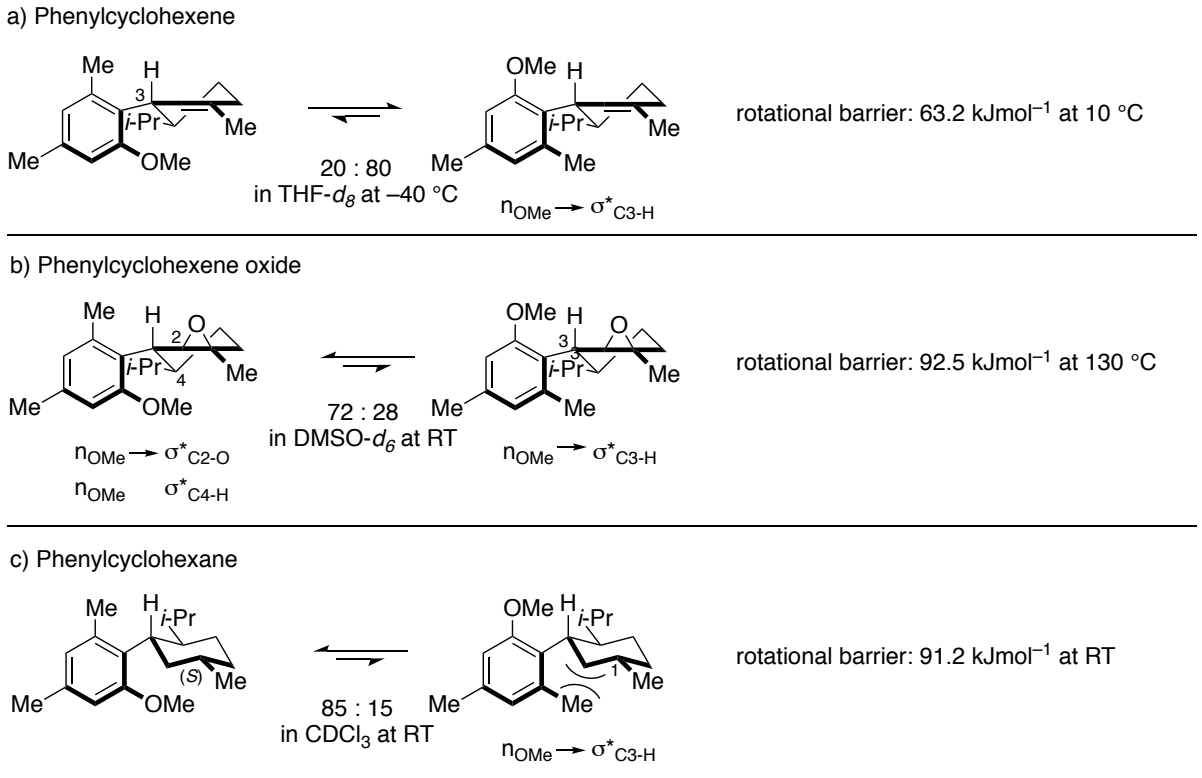
a calculated yield for the major diastereoisomer. However, the obtained yields exceeded a quantitative conversion which is only feasible if both diastereoisomers can be converted into the desired dihydrofuran (Scheme 23, a). A reasonable explanation for their observation was the occurrence of a restricted rotation about a Csp^2-Csp^3 axis resulting in diastereoisomers and even if only one conformation reacts to the product, the low rotational barrier allows complete conversion of both stereoisomers (Scheme 23, b).[88]



Scheme 23: a) Synthetic sequence in the total synthesis of (–)-Linderol revealing the existence of a rotationally restricted Csp^2-Csp^3 axis; b) Stereoisomers resulting from the restricted Csp^2-Csp^3 axis.

For a more detailed analysis of these rotational isomers, Berber together with Clayden investigated a series of cannabidiol and linderatin derivates to rationalize the configurational stabilities of these compounds through dynamic NMR studies (Scheme 24). During the examination of the ratio of rotational isomers in a series of phenyl cyclohexenes with different *ortho*-substituents on the aryl ring, the astonishingly high ratio of 20:80 in favor of one isomer was observed in comparison to the low difference in steric demand between the two investigated substituents. Thus, these two rotational isomers were examined in more detail by computational studies. The methoxy substituent was proposed having a stabilizing interaction from the lone pair into the σ^* orbital of the hydrogen in C3-position leading to the preference of one isomer. Nevertheless, the rotational barrier of only 63.2 $kJmol^{-1}$ is very low and isolation of the isomers for further analysis was impossible. (Scheme 24, a). Higher rotational stability was found for the series of phenyl cyclohexene oxides and a barrier to rotation of 92.5 $kJmol^{-1}$ was determined for the cyclohexane oxide congener. Thereby, an inversion of the ratio to 72:28 for the rotational isomers was observed.

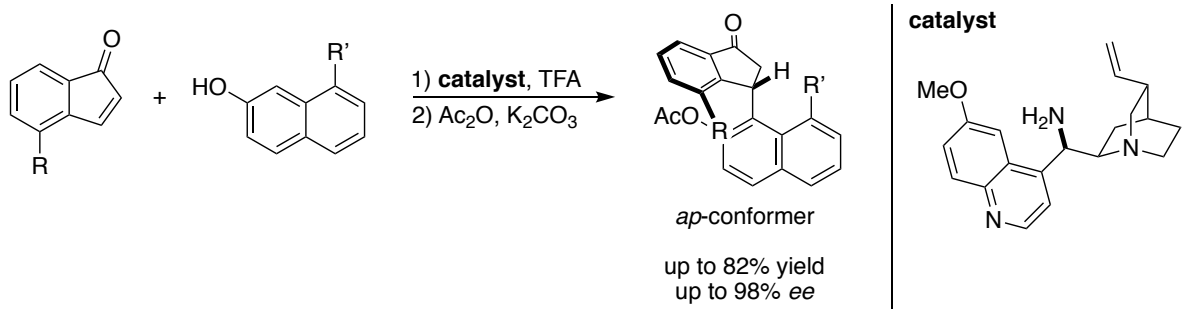
While the stabilizing n_{OMe} to $\sigma^*_{C3\text{-}H}$ interaction is favoring the minor isomer, other electronic effects are likely to stabilize the major isomer. Based on DFT calculations, the researchers proposed two crucial interactions of the methoxy function (n_{OMe} to $\sigma^*_{C2\text{-}O}$ and n_{OMe} to $\sigma^*_{C4\text{-}H}$), which together are more stabilizing than the n_{OMe} to $\sigma^*_{C3\text{-}H}$ of the minor isomer (Scheme 24, b).[89] Berber continued the investigation of rotational isomers with cannabidiol derivates that were obtained by hydrogenation of the cyclohexene to the cyclohexane ring, which occurred diastereoselectivly resulting in a (*S*)-configuration of the stereogenic carbon in the 1-position. The cyclohexane derivate exhibited with 91.2 kJmol^{-1} a comparably high configurational stability as the corresponding cyclohexene oxide and it was obtained in a ratio of 85:15. Compared to the electronic factors leading to a restricted rotation for the cyclohexene and cyclohexene oxide compounds, DFT calculations suggested steric interactions between the methyl substituent of the aryl and the C2 of the cyclohexane as the major influence on the rotational barrier. Furthermore, the barrier to rotation was approximately 20.1 kJmol^{-1} higher as for the 1-(*R*)-epimer of the cyclohexane (methyl group in axial position) suggesting that the rotational barrier is not only dependent on the *ortho*-substituents of the aryl group (Scheme 24, c).[90]



Scheme 24: Essential electronic interactions explaining the ratio of rotational isomers occurring from rotationally restricted Csp^2-Csp^3 single bonds.

1.5.7. Stereocenter Configuration Controlling Csp^2-Csp^3 Atropisomerism

The so far discussed studies all contained examples where the rotationally restricted axis was formed under substrate-controlled conditions and the obtained conformers were analyzed in detail to rationalize the configurational distribution of the substrate bias. However, one could imagine that in a system with high rotational barrier, the development of a catalyst-controlled stereoselective reaction is feasible. A related example of a methodology involving a catalyst for the preparation of compounds containing a rotationally restricted Csp^2-Csp^3 single bond, which was reported by the group Bencivenni.[91] A stereoselective Friedel-Crafts alkylation of β-naphthols with indenones catalyzed by a quinidine-derived organocatalyst controlled the configuration of a stereogenic center which influenced the conformation of the rotationally restricted Csp^2-Csp^3 single bond. With the introduction of bulky substituents on the 4-position of the indenone and in the 8-position of the β-naphthol, the reaction was highly selective and the (*ap*)-conformer was obtained as a single diastereoisomer in high yields and excellent enantioselectivity (Scheme 25).



Scheme 25: Stereoselective Friedel-Crafts alkylation to prepare the (*ap*)-conformer of a rotationally restricted Csp^2-Csp^3 single bond.

It is important to note that in this method the catalyst controls the configuration of the stereocenter. The configuration of the stereogenic axis then adapts the preferred configuration controlled by the stereocenter in close proximity by a dynamic resolution under thermodynamic conditions favoring the (*ap*)-conformer. This notion was supported by DFT computation that revealed an energy difference of 16.7 $kJmol^{-1}$ between the (*sp*)- and the (*ap*)-conformer of their model compound (R = Br, R' = NHBoc). Furthermore, a rotational barrier of 105.5 $kJmol^{-1}$ was calculated for the interconversion of the (*ap*)- into the (*sp*)-conformer. Thus, the barrier to interconversion from the (*sp*)- into the (*ap*)-conformer is 88.8 $kJmol^{-1}$, which is low enough for a complete interconversion into the more stable (*ap*)-conformer within the reaction time of 56 hours at 20 °C (Figure 13).

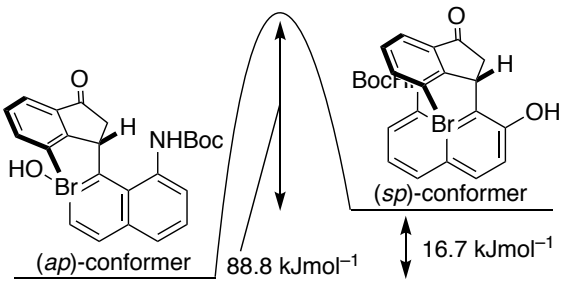
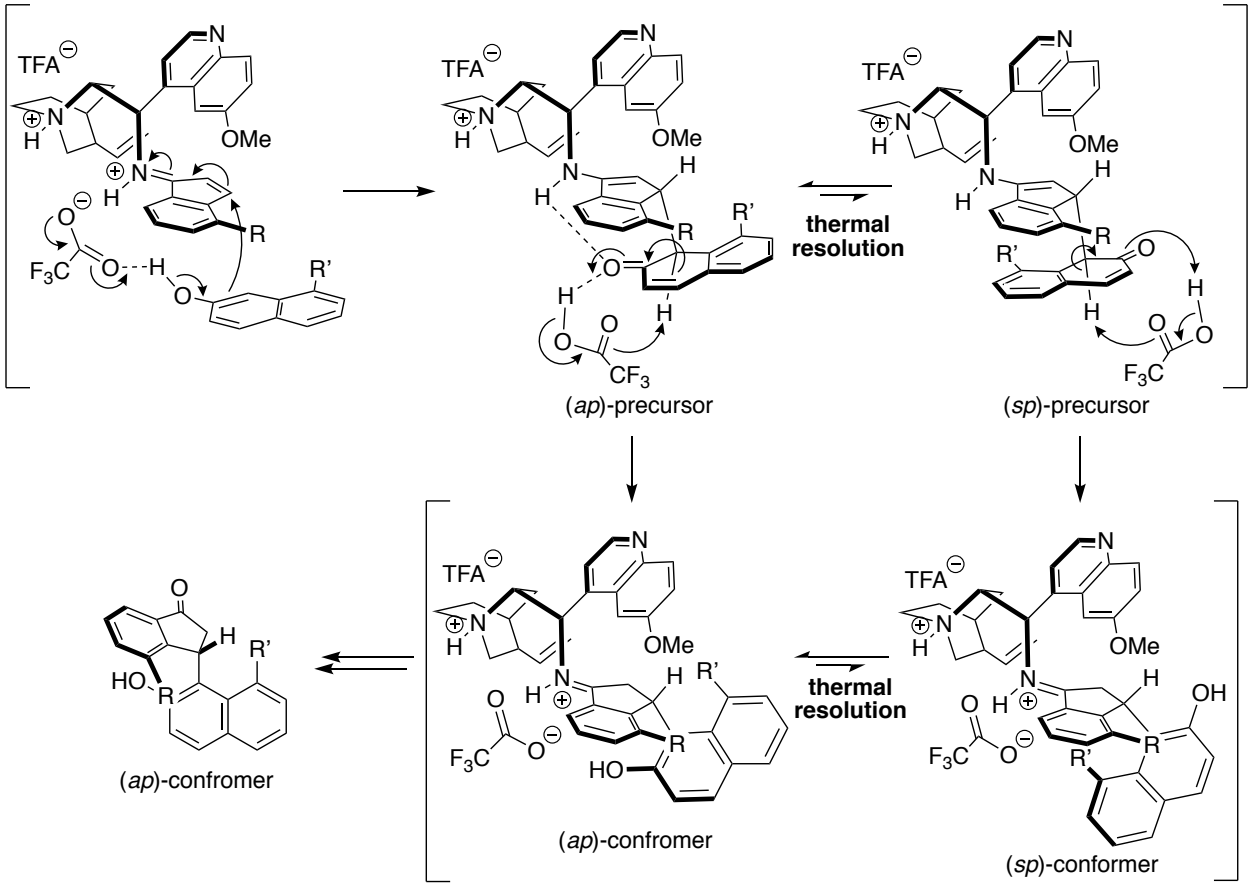


Figure 13: Rotational barrier for the thermodynamic resolution of the rotational isomers.

Concerning the mechanism, the researchers proposed the activation of the indenone through formation of the iminium species with the catalyst. TFA then triggers the attack of the β-naphthol in a Michael addition to the activated indenone in a *Si*-face attack. The obtained Csp^3-Csp^3 atropisomer was suggested to preferentially arrange in an orientation leading to the formation of the (*ap*)-conformer upon dehydration through a stabilizing hydrogen-bond formation with the quinidine type catalyst. Interconversion of the Csp^3-Csp^3 atropisomers at this stage was proposed to be possible favoring the (*ap*)-precursor. The TFA promoted dehydration forms either the (*ap*)- or the (*sp*)-conformers, whilst the (*sp*)-conformer is interconverting into the (*ap*)-conformer resulting in the final and exclusive formation of the configurationally more stable (*ap*)-conformer. Hydrolysis of the iminium releases the catalyst and the Csp^2-Csp^3 atropisomeric product is released (Scheme 26).



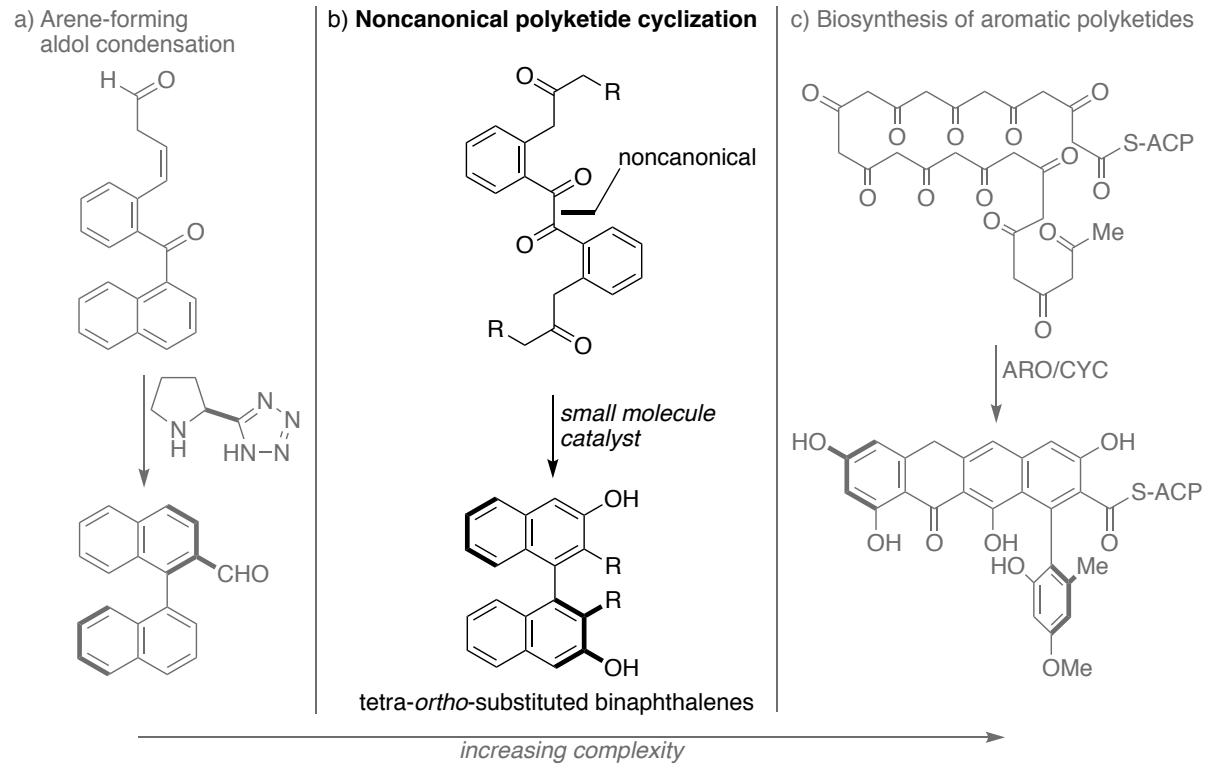
Scheme 26: Proposed mechanism for the catalyst-controlled Friedel-Crafts alkylation followed by the thermodynamic resolution of the rotationally restricted Csp^2-Csp^3 axis.

This interesting example showcases the ability to obtain exclusively one out of more than two stereoisomers resulting from a molecule containing a Csp^2-Csp^3 stereogenic axis. Nevertheless, the catalyst controls the configuration of a stereocenter in close proximity to the Csp^2-Csp^3 axis, which then adopts a preferred configuration through a thermal resolution. A method where the catalyst controls the rotationally restricted Csp^2-Csp^3 single bond as the only stereogenic element of a molecule remained unexplored.

2. Objective

2.1. Noncanonical Polyketide Cyclization

Inspired by the aromatic polyketide biosynthesis, our group developed an atroposelective arene-forming aldol condensation which emerged to an effective method for the stereoselective preparation of various rotationally restricted compounds (Scheme 27, a). In contrast to the natural poly-β-carbonyl substrates (Scheme 27, c), the starting materials previously possessed only one nucleophilic α-position and one electrophilic carbonyl function. We thus envisioned to explore the ability of small-molecule catalysts to selectively cyclize poly-carbonyl substrates with more than one cyclization possibility by examining a transformation more closely related to the biosynthesis of aromatic polyketides (Scheme 27, b).

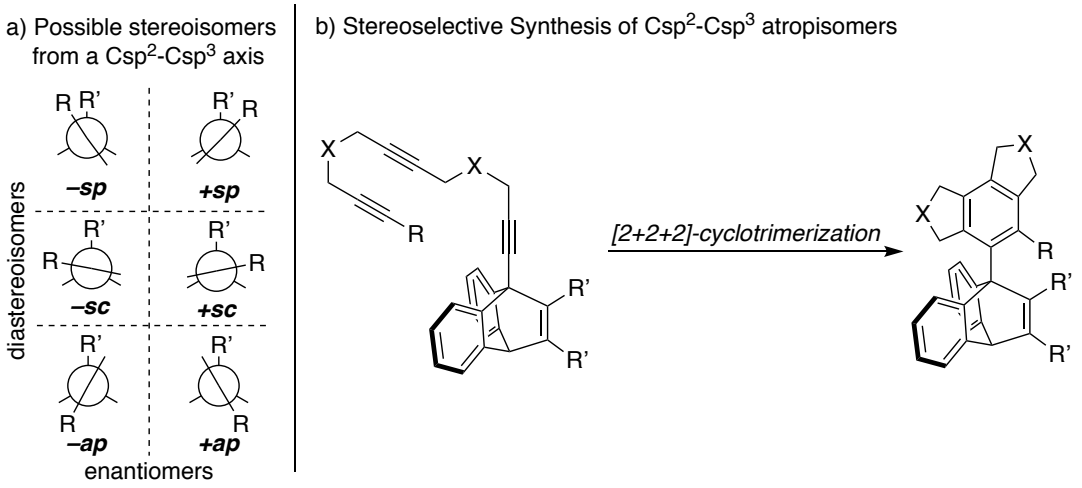


Scheme 27: a) Established arene-forming aldol condensation reported by our group; b) Anticipated noncanonical polyketide cyclization; c) Example for the biosynthesis of aromatic polyketides.

By increasing the complexity of the aldol methodology, we intended to develop a double arene-forming aldol condensation with a substrate bearing at least four carbonyl functions. Regarding the substrate design, the interruption of the β-oxygenation pattern with a 1,2-diketone (= noncanonical) was anticipated to give rise to atropisomeric binaphthalenes distinct from oxidative dimerization products. The thereby accessible tetra-*ortho*-substituted biaryls containing hydroxy functions in the 3,3'-position represent a privileged scaffold in catalysis and eventually enable an alternative synthetic route to scarcely accessible ligands and catalysts. The prospects of mimicking the polyketide synthase enzyme machinery by small-molecule catalysts encouraged us to develop a synthetic access to poly-carbonyl substrates and explore their catalyst controlled cyclizations.

2.2. Stereoselective Synthesis of Csp^2-Csp^3 Atropisomers

Beyond the well-established biaryl atropisomers which are today frequently seen in ligands and catalysts, stereoisomers resulting from a restricted rotation about a single bond including at least one tetrahedral carbon are much less explored. This unique stereochemical arrangement results in an exclusive setting with enantiomers and diastereoisomers arising from only one stereogenic element ($>2^n$). Hence, the intriguing number of six stereoisomers can result from the restricted rotation about a Csp^2-Csp^3 single bond (Scheme 28, a).[73] More generally, a catalyst-controlled stereoselective synthesis that controls one stereogenic element for one out of >2 stereoisomers is not yet precedented. We thus envisioned to develop a methodology for the first stereoselective synthesis of $>2^n$ stereoisomers by exploring Csp^2-Csp^3 atropisomers (Scheme 28, b).



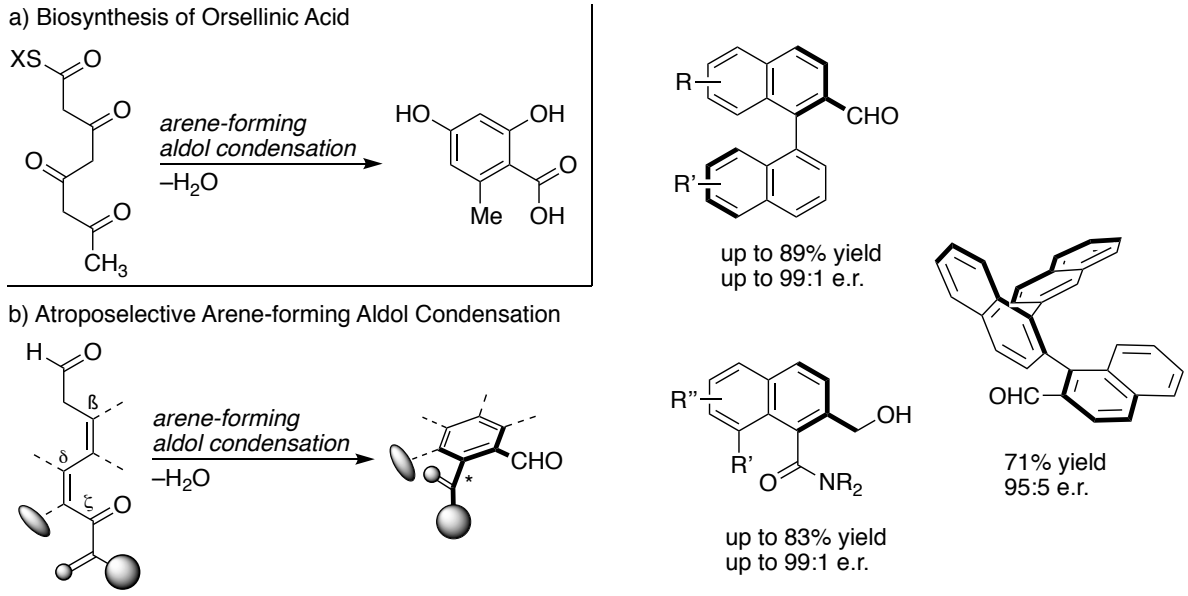
Scheme 28: a) Three enantiomeric pairs of diastereoisomers result from a rotationally restricted Csp^2-Csp^3 single bond; b) Envisioned [2+2+2]-cyclotrimerization for the stereoselective preparation of Csp^2-Csp^3 atropisomers.

A [2+2+2]-cyclotrimerization was anticipated as ideal reaction due to the high tolerance towards steric demand and the modularity of the required trialkyne substrates. Receiving atropisomeric products containing a restricted Csp^2-Csp^3 axis with sufficient configurational stability will be crucial for the development of an atroposelective methodology. Thus, the recognition of the essential steric interactions which leads to high rotational barrier will help to design and synthesize a suitable substrate for our objective. After having established a suitable substrate providing configurationally stable products, variation of the ligand or catalysts ideally allow to access all three possible diastereoisomers with high atroposelectivites.

3. Noncanonical Polyketide Cyclization

3.1. Atroposelective Arene-forming Aldol Condensation

Aromatic polyketides are a diverse class of natural products with promising biological activities as anti-cancer agents, antibiotics or cholesterol-lowering agents and thus are of great interest for medicinal chemistry. Besides their interesting properties, Nature evolved an intriguing pathway in order to construct these natural products. The myriad of aromatic compounds of this family of natural products is derived from simple acetate units. In the biosynthetic pathway, the acetate building blocks are assembled to highly reactive poly-β-carbonyl chains which are diversified into a countless number of polyketide natural products through selective cyclizations controlled by polyketide synthase machineries.[6–7] Aromatic polyketides are presumably obtained through arene-forming aldol condensations of non-reduced poly-β-carbonyl chains exemplified by the biosynthesis of orsellinic acid (Scheme 29, a). Inspired by polyketide biosynthesis, our group developed an arene-forming aldol condensation for the synthesis of rotationally restricted aromatic compounds.[67–68] A small-molecule catalyzed 6-(enol*endo*)-*exo*-*trig* cyclization followed by a dehydration resulted in the *de novo* construction of an aromatic ring. Two different substituents in the terminal position lead to the formation of a rotationally restricted biaryl bond in which the configuration can be efficiently controlled by primary and secondary amine catalysts. This biomimetic methodology enabled the atroposelective preparation of binaphthalene carbaldehydes,[69] axially chiral aromatic amides[71] and configurationally stable oligo-1,2-naphthylenes[70] in high yields and excellent selectivities (Scheme 29, b).



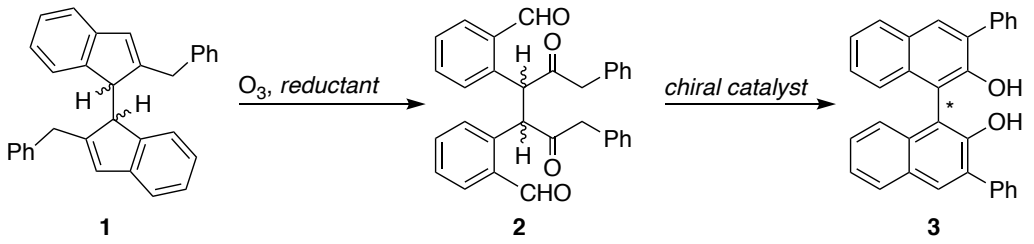
Scheme 29: a) Biosynthesis of orsellinic acid. b) Atroposelective arene-forming aldol condensation for the preparation of rotationally restricted binaphthalene carbaldehydes, axially chiral aromatic amides and configurationally stable oligo-1,2-naphthylenes.

Two carbonyl functions of the substrates were replaced by an olefin and an aryl moiety resulting in a β,δ-unsaturated aldehyde as substrate which is well-defined to cyclize intramolecular in a 6-(enol*endo*)-*exo*-*trig* cyclization with the ketone in the ζ-position. Pursuing the endeavor to mimick the enzymatic machineries of the polyketide biosynthesis by small-molecule catalysts, we intended to investigate selective cyclizations of substrates bearing more than two carbonyl functions, thus more closely representing the natural poly-β-carbonyl chains. Therefore, we envisioned to prepare a poly-carbonyl substrate, which is converted in polyketide type cyclizations into a rotationally restricted biaryl product upon addition of suitable small-molecule catalysts.

3.2. Examination of Biindenes

For the investigation of polyketide cyclizations, a substrate bearing at least four carbonyl functions is required. Already the former substrates bearing one aldehyde and one ketone for the arene-forming aldol condensation were sensitive and had to be kept in solution after preparation to prevent spontaneous cyclizations. Therefore, an efficient method for a late stage introduction of the carbonyl functions is necessary. An ozonolysis reaction seemed especially practical, as up to two carbonyl functions per converted olefin are potentially obtained and the conversion of multiple olefins might allow the installation of all carbonyl moieties in one step. With these considerations

in mind, we envisioned to convert the biindene **1** in a two-fold ozonolysis into the poly-carbonyl substrate **2** to investigate the selectivity of the cyclization modes by small-molecule catalysts. A catalyst-controlled double 6-(enol*endo*)-*exo-trig* cyclization[92] and subsequent dehydration would yield the 3,3'-substituted binaphthol **3**, a highly valuable scaffold in catalyst design. However, the two additional carbonyl units enable multiple other cyclizations such as the formation of five- and seven-membered carbocycles as well as numerous heterocycles incorporating oxygen atoms. Thus, controlled cyclizations with a catalyst are required to obtain the binaphthol product **3** (Scheme 30).

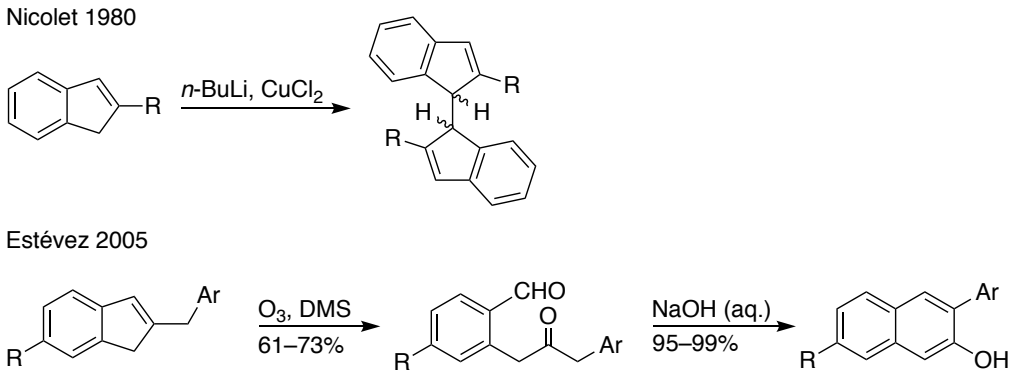


Scheme 30: Intended two-fold ozonolysis to convert biindene **1** into the poly-carbonyl substrate **2**. A double 6-(enol*endo*)-*exo-trig* cyclization of **2** would lead to the 3,3'-substituted binaphthol **3**.

To test the feasibility of the ozonolysis reaction for the preparation of the poly-carbonyl substrate **2** and to explore the catalyst-controlled cyclizations, a synthetic route to access the biindene **1** had to be developed.

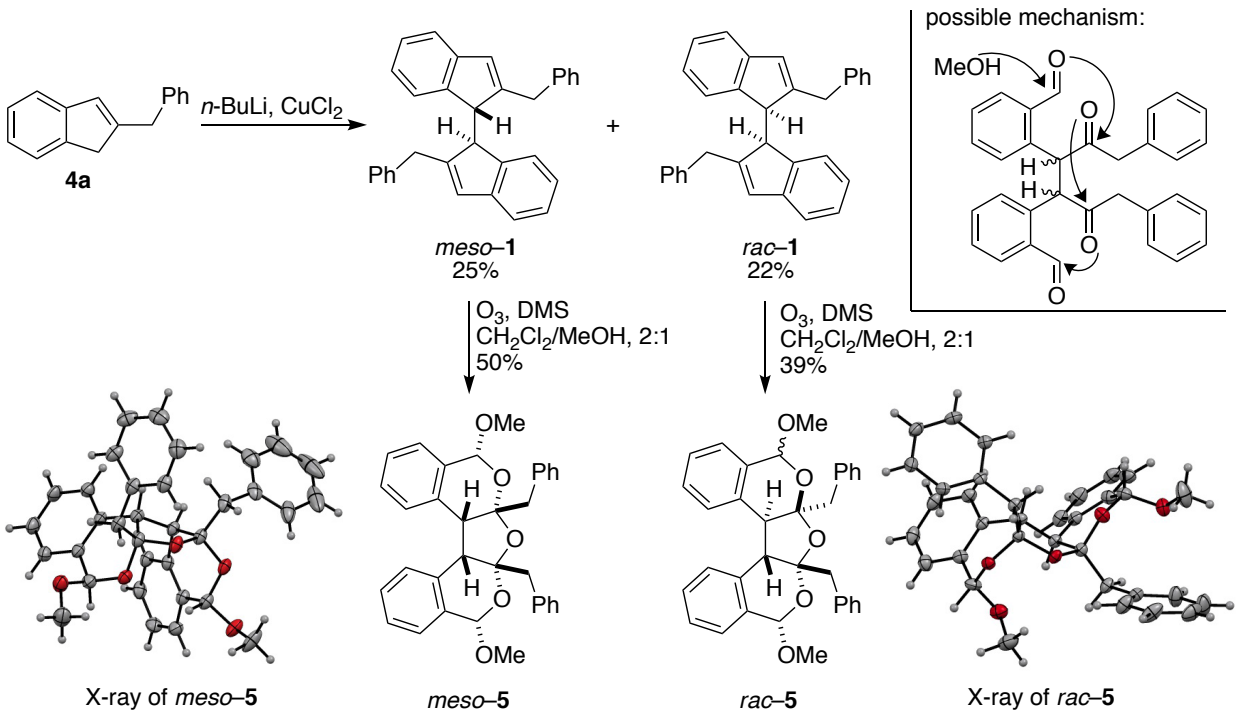
3.2.1. 1*H*,1*H*'-Biindenes

For the design of a synthetic route of the benzyl biindene **1** as precursor for the two-fold ozonolysis, we could profit from a literature procedure using *n*-BuLi and copper chloride for the oxidative dimerization of indenes developed in the group of Nicolet.[93] Additionally, the ozonolysis reaction of indenes has been used by the group of Estévez for the preparation of the corresponding keto aldehydes which were cyclized into naphthols under basic conditions, demonstrating the viability of 6-*(enolendo)-exo-trig* cyclizations with these keto aldehyde structures (Scheme 31).[94] With our notion being supported by this literature reports, we initiated our project with the preparation of biindene **1**.



Scheme 31: Oxidative dimerization of indenes developed by the group of Nicolet.[93] Ozonolysis and aldol condensation sequence to prepare 2-substituted naphthols developed by Estévez and co-workers.[94]

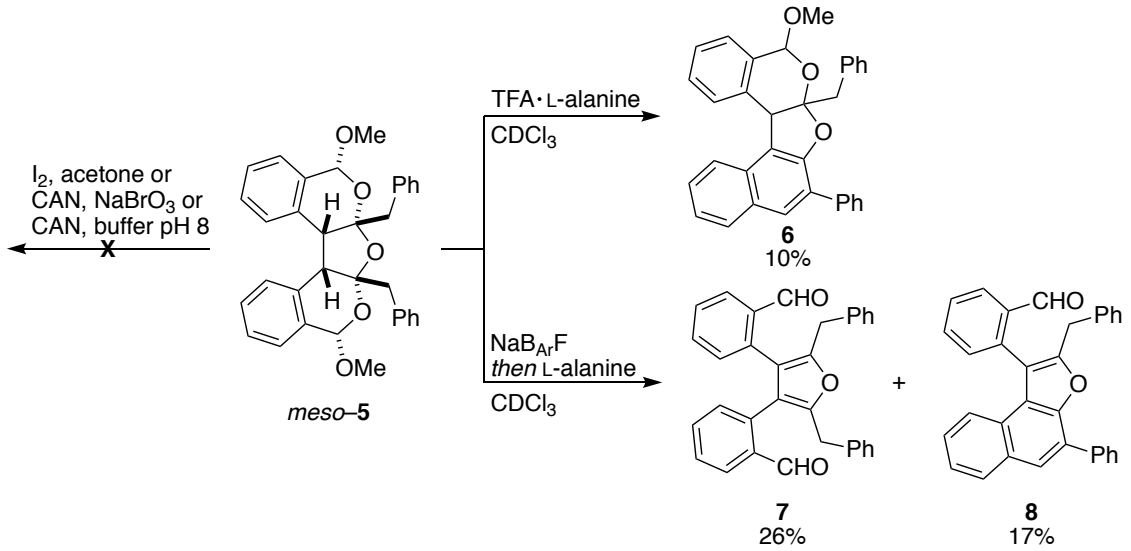
The benzyl indene monomer **4a** which was required for the oxidative dimerization protocol was efficiently prepared through a literature known protocol from 1-indanone and benzaldehyde.[94] Under slightly modified conditions, the oxidative dimerization of benzyl indene **4a** yielded the biindene as a diastereomeric mixture in an overall yield of 65% (25% *meso*-**1**, 22% *rac*-**1** and 18% as a mixture of both). With the pure biindenes *meso*-**1** and *rac*-**1** in hand, the two-fold ozonolysis was investigated. Performing the ozonolysis in dichloromethane with various reducing agents resulted in a complex mixture of products. Changing the solvent to a 2:1 mixture of dichloromethane and methanol yielded one major product for each precursor, however the desired keto aldehyde **2** was not obtained. The two main products were found to be the multi acetal products *meso*-**5** and *rac*-**5**. The rather unusual structures of *meso*-**5** and *rac*-**5** containing four consecutive acetals was confirmed by X-ray analysis of both compounds. The four consecutive acetals are putatively formed in a cascade reaction initiated by the attack of a methanol molecule to an aldehyde. The finally obtained hemiacetal is further converted into the more stable acetal by the substitution of a second molecule of methanol resulting in *meso*-**5** or *rac*-**5** (Scheme 32).



Scheme 32: Oxidative dimerization of benzyl indene **4a** and ozonolysis of the obtained biindenes *meso*-**1** and *rac*-**1** yielding the acetals *meso*-**5** and *rac*-**5**.

If the proposed mechanism for the formation of the consecutive acetals is operational, it becomes evident, that the desired keto aldehyde substrate **2** must have been formed during the ozonolysis in order to obtain the acetals *meso*-**5** and *rac*-**5**. Additionally, *meso*-**5** and *rac*-**5** are stabilized forms of the tetra-carbonyl substrates **2**. If the acetal groups are cleavable under conditions that do not trigger an uncatalyzed cyclization, the acetal formation would be a useful strategy to isolate and purify the keto aldehyde substrate **2** after the two-fold ozonolysis. Therefore, mild conditions for the acetal cleavage were investigated. The acetal groups of *meso*-**5** were found being remarkably stable and no conversion was observed with catalytic amounts of iodine,[95] with cerium ammonium nitrate at pH 8 or in combination with sodium bromate.[96] A promising one-fold arene-forming aldol condensation occurred under acidic conditions by using the TFA salt of L-alanine. Instead of a second arene-forming aldol condensation, the reformation of a two-fold acetal induced by the newly formed naphthol occurred, as confirmed with the isolation **6** in 10% yield. *meso*-**5** was completely consumed with catalytic amounts of $NaB_{Ar}F$[97] and after the addition of L-alanine, the furan **7** was isolated in 26% yield together with the naphthofuran **8** in 17% yield. An intramolecular condensation of the two ketones of **2** results in the formation of the furan **7**. The naphthofuran **8** is formed through an arene-forming aldol condensation according to the mechanism towards **6** and

this time the hemiacetal is dehydrated to the naphthofuran **8** instead of the acetal formation towards **6** (Scheme 33).



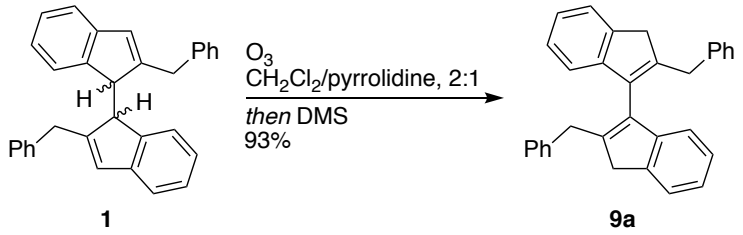
Scheme 33: Attempts to cleave the acetals of *meso*-**5** and conversion of *meso*-**5** into diacetal **6**, furan **7** and naphthofuran **8**.

The isolation of the cyclization products **6**, **7** and **8** underlined the versatility of the possible cyclization modes as well as the difficulties to control the reactivity of a compound with multiple carbonyl functions in close proximity. Even though the isolation of the keto aldehyde substrate **2** in the protected form as *meso*-**5** and *rac*-**5** appeared as advantageous, finding the adequate conditions to cleave the acetals and simultaneously induce a double 6-*(*enol*endo)-exo-trig* cyclization was found to be challenging. Therefore, we considered to reinvestigate the ozonolysis without methanol as co-solvent to prevent the acetal formation. Instead, an immediate conversion of the substrate **2** might be possible if a catalyst is already in the reaction mixture for the ozonolysis.

3.2.2. Olefin Isomerization

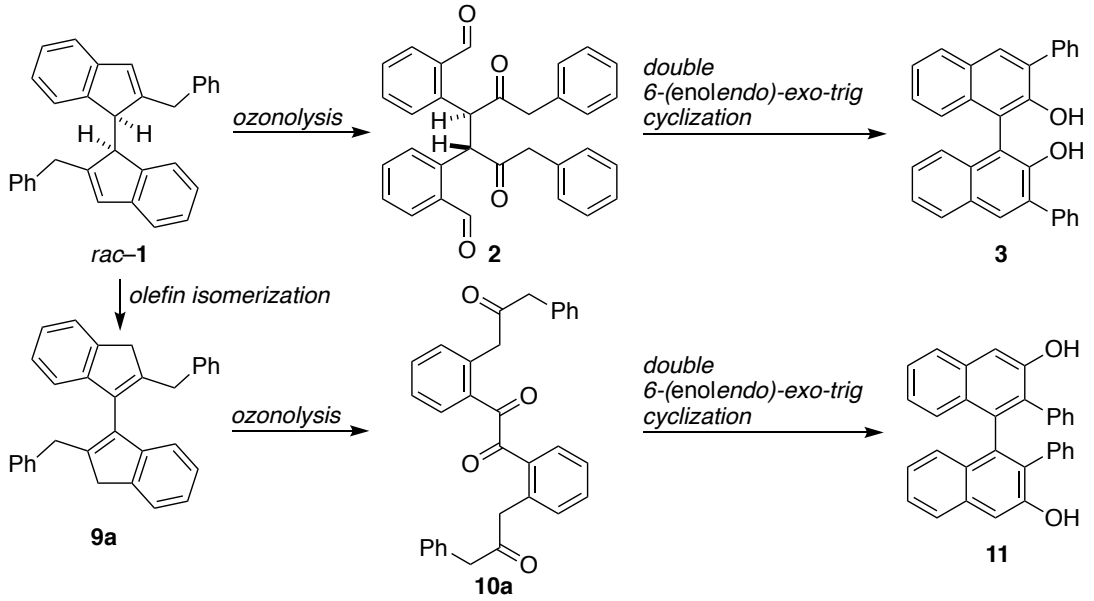
Pyrrolidine was chosen as the catalyst to examine the direct conversion of the keto aldehyde **2** after its formation in the ozonolysis. Hence, an ozonolysis reaction was performed in a 2:1 mixture of dichloromethane and pyrrolidine. Surprisingly, instead of the oxidative cleavage with ozone, isomerization of the olefins to the more stable 3*H*,3'*H*-biindene **9a** was observed in an excellent yield of 93%. Presumably, the oxidation of pyrrolidine to the N-oxide by ozone was faster than the

oxidative cleavage of the isomerized tetra-substituted olefins which allowed the isolation of **9a** in high yields (Scheme 34).[a]



Scheme 34: Isomerization of the 1*H*,1'*H*-biindene **1** to the 3*H*,3'*H*-biindene **9a** induced by pyrrolidine.

The observed olefin isomerization is a great opportunity since it enables the conversion of the diastereomeric mixture *rac*-**1** and *meso*-**1** into one single compound **9a**. More importantly, the tetra-carbonyl substrate **10a** resulting from the ozonolysis of **9a** would contain four ketones and is therefore expected to be less reactive and more practical to handle than **2**. Furthermore, the formation of consecutive acetals is no longer possible with the 1,2-diketone of **10a,** but a double 6-*(*enol*endo)-exo-trig* cyclization is feasible resulting in a binaphthalenes scaffold **11** with a reversed substitution pattern compared to cyclization product from keto aldehyde **2**. (Scheme 35).

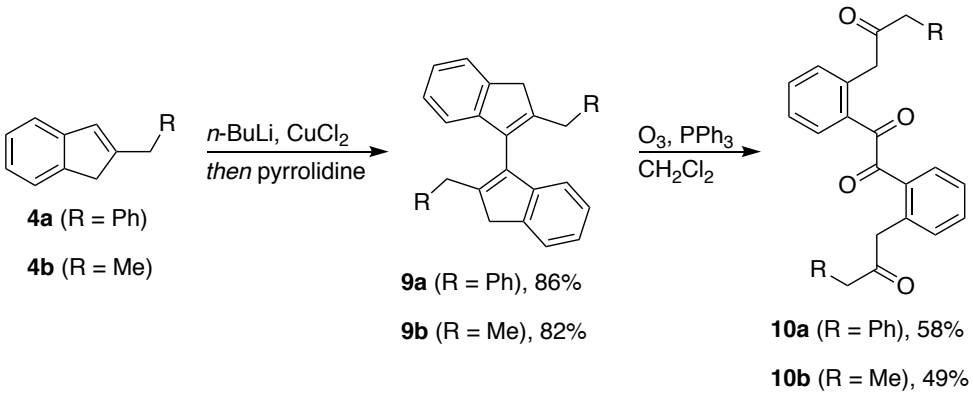


Scheme 35: A double 6-*(*enol*endo)-exo-trig* cyclization of the substrate **2** would lead to the formation of a 3,3'-diarylated binaphthol, while a double 6-*(*enol*endo)-exo-trig* cyclization of tetra-ketone **10a** results in a binaphthalene product **11** with a reversed substitution pattern compared to **3**.

[a] Nicolet and co-workers described a similar olefin isomerization of biindenes under more forcing condition using a mixture of triethylamine and pyridine at elevated temperatures.[93]

3.2.3. 3*H*,3*H*'-Biindenes

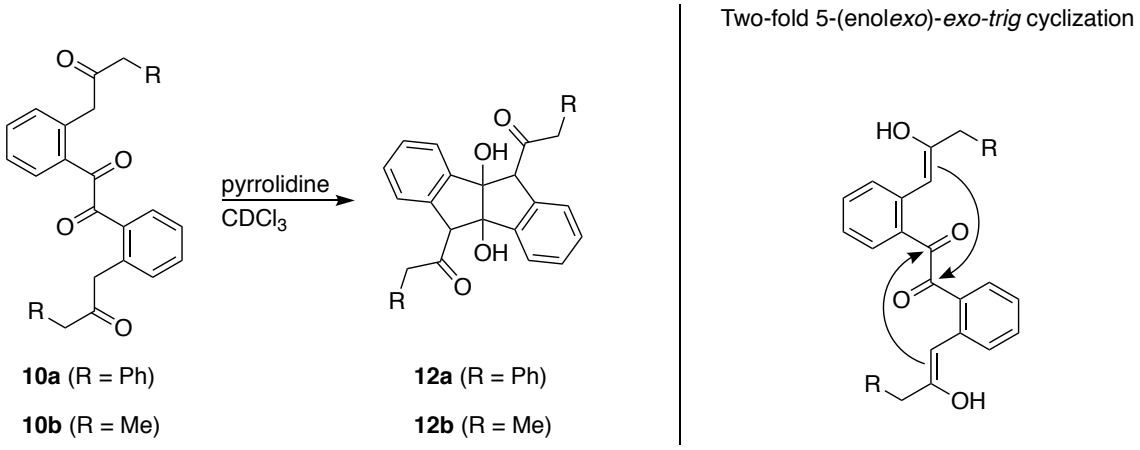
To explore the reactivity of the tetra-ketone **10a**, the two-fold ozonolysis of the 3*H,*3'*H*-biindene **9a** had to be investigated first. Accordingly, **9a** was resynthesized from the benzyl indene **4a** through the oxidative dimerization followed by the olefin isomerization in a good yield of 86% over two steps. In parallel, an ethyl-substituted biindene **9b** was prepared with the same protocol in 82% yield in order to investigate the influence of an alkyl substituent on the cyclization modes. Initial investigations of the ozonolysis of biindenes **9a** and **9b** using dimethyl sulfide as a reducing agent resulted in a complex mixture of different compounds. PPh_3 was found being an efficient reductant and both tetra-ketones **10a** and **10b** were obtained in 58% and 49% yield. As hypothesized, the tetra-ketones **10a** and **10b** were less reactive and could be isolated by column chromatography, which allowed a more convenient investigation of the cyclizations compared to the previous substrate **2** (Scheme 36).



Scheme 36: Dimerization and olefin isomerization followed by the oxidative cleavage of the olefins with ozone to obtain the tetra-ketone substrates **10a** and **10b**.

With both tetra-ketones **10a** and **10b** in hand, the reactivity of the substrates in the cyclization reactions was examined. The pyrrolidinyl-tetrazole catalyst[98–100] and a Jørgensen-type catalyst[101] were examined first, but no conversion was observed for both. In contrast, the substrates **10a** and **10b** were fully converted by using sodium hydroxide and (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine, but a complex mixture of products was obtained. Even though one major product was formed with basic aluminum oxide and aqueous potassium hydroxide, the instability of the formed product prohibited the characterization. Gratifyingly, pyrrolidine was found to efficiently trigger the cyclizations to the same product and quantitative conversion of **10a** to the previously observed major compound was obtained in only 30 min. By the absence of side-product formation, the crude

product was analyzed, disclosing the formation of the hydropentalene **12a** by a double 5-*(*enol*exo)-exo-trig* cyclization. Regarding the reactivity of tetra-ketone **10a**, both enol tautomers are stabilized through a phenyl ring in the α-position, but the exclusive formation of the hydropentalene emphasized the preference for the 5-*(*enol*exo)-exo-trig* cyclization. For the methyl-substituted tetra-ketone **10b,** only the enolate leading to the 5-*(*enol*exo)-exo-trig* cyclization is stabilized through a phenyl ring and it was therefore not surprising, that pyrrolidine entirely triggered the formation of the hydropentalene **12b** (Scheme 37).



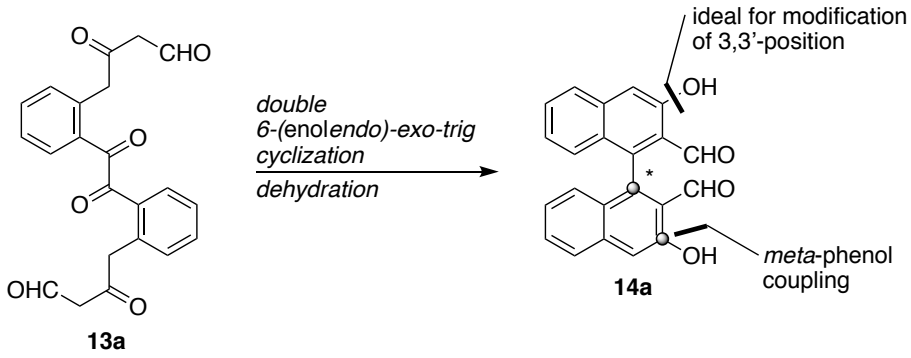
Scheme 37: 5-*(*Enol*exo)-exo-trig* cyclization of the tetra-ketone substrates **10a** and **10b** induced by pyrrolidine.

The quantitative formation of the hydropentalenes **12a** and **12b** demonstrated that selective cyclizations catalyzed by small-molecule catalysts are possible. Furthermore, the oxidative cleavage of biindenes by ozonolysis proved to be an efficient method for the preparation of poly-carbonyl compounds. With the tetra-ketone scaffold, an ideal basis is established to investigate catalyst-controlled polyketide cyclizations.

3.2.4. The Noncanonical Hexa-carbonyl Substrate

Analogous to the biosynthesis of aromatic polyketides, the most promising strategy to further activate the tetra-ketone substrate to favor 6-(enol*endo*)-*exo-trig* cyclizations appeared to be the replacement of the terminal phenyl- or methyl units with two additional carbonyl functions, since the proton in α-position of two carbonyl functions is significantly more acidic and thus more reactive than a proton in benzylic position. The introduction of two additional aldehydes was considered as ideal due to their applicability for secondary amine catalysis. A two-fold 6-

*(*enol*endo)-exo-trig* cyclization[b] of the intended hexa-carbonyl substrate **13a** eventually results in the formation of a tetra-*ortho*-substituted binaphthalene dicarbaldehyde **14a**. This noncanonical[102] hexa-carbonyl substrate contains an interrupted β-oxygenation pattern through a 1,2-diketone unit. A noncanonical polyketide cyclization (double arene-forming aldol condensation) would lead to a structurally unique scaffold consisting of two *meta*-connected naphthols distinct from oxidative dimerization processes generally leading to *ortho*- and *para*-phenol couplings.[60,63] Additionally, the privileged 3,3'-diarylated binaphthalene core is readily accessible from **14a** through a triflation and cross-coupling sequence (Scheme 38). [103]



Scheme 38: The noncanonical hexa-carbonyl substrate **13a** for the double arene-forming aldol condensation to access the binaphthalene dicarbaldehyde **14a**.

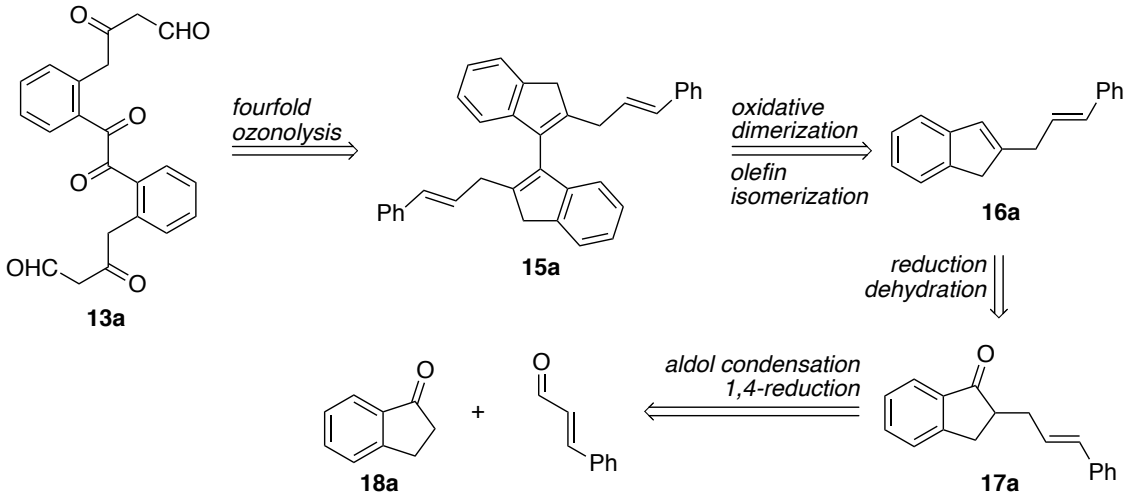
3.2.5. Precursor Synthesis

The most direct strategy to introduce the two additional aldehydes would be a four-fold ozonolysis of a biindene bearing two additional olefins in the side chain. Different to the previous ozonolysis reactions, these additional olefins are not cyclic and therefore two additional carbonyl compounds will be released in the oxidative cleavage besides the substrate. While a terminal olefin would lead to the formation of reactive formaldehyde, we planned to introduce cinnamyl moieties resulting in the liberation of considerably less reactive benzaldehyde.

From a retrosynthetic perspective, the hexa-carbonyl substrate **13a** would therefore be derived from the four-fold ozonolysis of cinnamyl biindene **15a**, accessed as the previous biindenes through an oxidative dimerization and olefin isomerization sequence. The cinnamyl indene monomer **16a** is derived from the literature known cinnamyl indanone **17a**[104] obtained through a ketone reduction and dehydration. Instead of the reported challenging α-alkylation of 1-indanone **18a** with cinnamyl

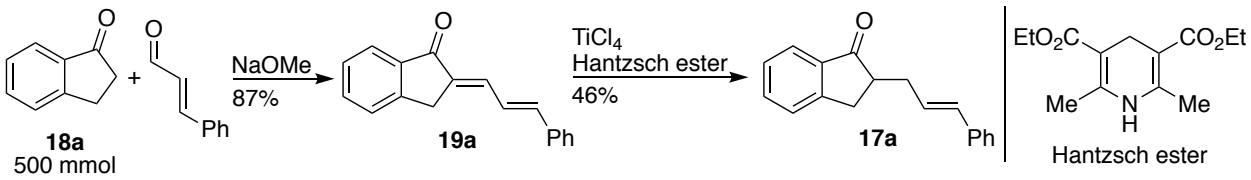
[b] 6-(enol*endo)-exo-trig* with respect to the keto-functionality

chloride,[104] we planned to synthesize the cinnamyl indanone **17a** through an aldol condensation of 1-indanone **18a** and cinnamyl aldehyde followed by a 1,4-reduction to avoid the undesired double alkylation (Scheme 39).



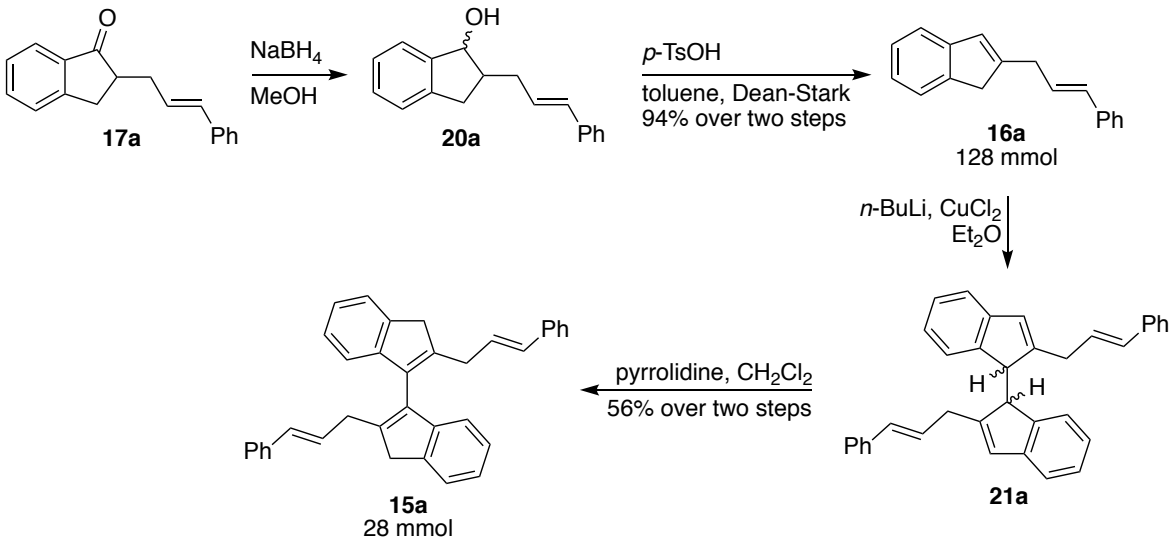
Scheme 39: Retrosynthetic analysis of the hexa-carbonyl substrate **13a**.

The substrate synthesis was initiated with the aldol condensation of 1-indanone **18a** and cinnamyl aldehyde which proceeded efficiently in methanol with catalytic amounts of sodium methoxide. The product **19a** precipitated directly from the reaction mixture allowing to perform the reaction effortlessly on a 500 mmol scale in 87% yield. In small scale test reactions, high selectivity was obtained in the 1,4-reduction with a combination of lithium aluminum hydride and copper iodide,[105] but the outcome was very inconsistent and generally low yielding when scaled up. Examination of various literature known procedures revealed the utility of a method developed by the group of Lam using titanium tetrachloride and Hantzsch ester as a hydride source.[106] No 1,2-reduction and only traces of 1,6-reduction were observed under these conditions. The moderate yield of 46% is attributed to difficulties in the purification of the 300 mmol scale reaction by column chromatography rather than the reaction itself (Scheme 40).



Scheme 40: Aldol condensation of 1-indanone and cinnamyl aldehyde followed by the regioselective 1,4-reduction of **19a** to the cinnamyl indanone **17a**.

To obtain the cinnamyl indene monomer **16a**, the carbonyl function of cinnamyl indanone **17a** was reduced with sodium borohydride in methanol and the resulting diastereomeric mixture of alcohols **20a** was dehydrated under acidic conditions in toluene at elevated temperatures to form the cinnamyl indene **16a** in an excellent yield of 94% over two steps. The oxidative dimerization was performed under the previously established conditions using *n*-BuLi and copper chloride (section 3.2.3). Finally, the cinnamyl biindene **15a** was isolated after the olefin isomerization of **21a** induced by pyrrolidine yielding the precursor **15a** in 56% yield over two steps. A scale up of this sequence enabled the preparation of 13 g (28 mmol) of **15a** in one single batch (Scheme 41).



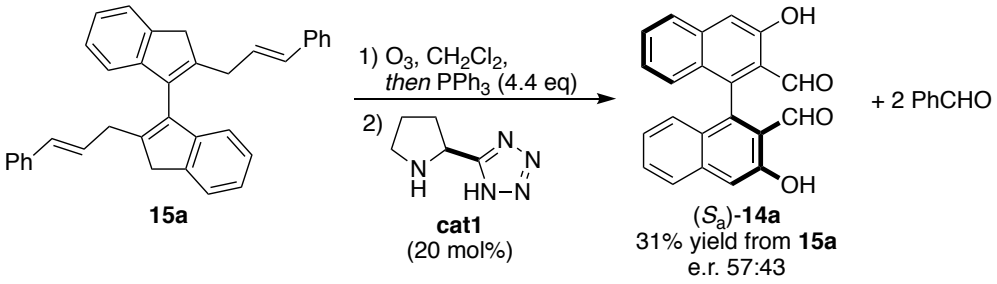
Scheme 41: Synthesis of the precursor **15a** from cinnamyl indanone **17a** through reduction and dehydration to the indene **16a** followed by oxidative dimerization and olefin isomerization.

After the development of an efficient synthesis of cinnamyl biindene **15a**, the final preparation of the anticipated hexa-carbonyl substrate **13a** through the four-fold ozonolysis and the intended double arene-forming aldol condensation was examined.

3.3. Optimization of the Ozonolysis and the Noncanonical Polyketide Cyclization

As a starting point for the investigations of the four-fold ozonolysis, the initial conditions for the preparation of tetra-ketones **10a** and **10b** were used. Hence, the ozonolysis was performed in dichloromethane at low temperatures and with PPh_3 as reducing agent. Full consumption of the substrate **15a** was observed, but the hexa-carbonyl substrate **13a** could not be isolated. Stability tests indicated that the ozonolysis products are instable on silica. Consequently, investigations of

the cyclizations had to be explored with the unpurified substrate solution from the ozonolysis. Thus, the pyrrolidinyl-tetrazole catalyst **cat1** was added to the crude reaction mixture of the ozonolysis and we were delighted to observe that the desired binaphthalene dicarbaldehyde **14a** was obtained in an overall yield of 31% from the precursor **15a** and with an atroposelectivity of 57:43. The remarkably high overall yield demonstrates the ability of small-molecule catalysts to selectively trigger polyketide cyclizations mimicking polyketide synthases. Furthermore, the small enantiomeric excess of the binaphthalene product **14a** indicated the feasibility to control the stereogenic axis through small-molecule catalysts in this reaction (Scheme 42).



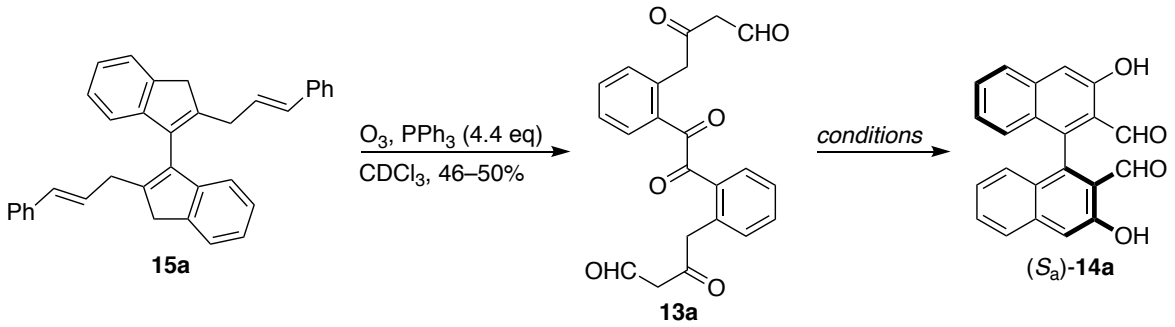
Scheme 42: Four-fold ozonolysis of the biindene **15a** followed by the noncanonical polyketide cyclization catalyzed by the pyrrolidinyl-tetrazole catalyst **cat1** yielding the binaphthalene product **14a** in a first promising atroposelectivity of 57:43.

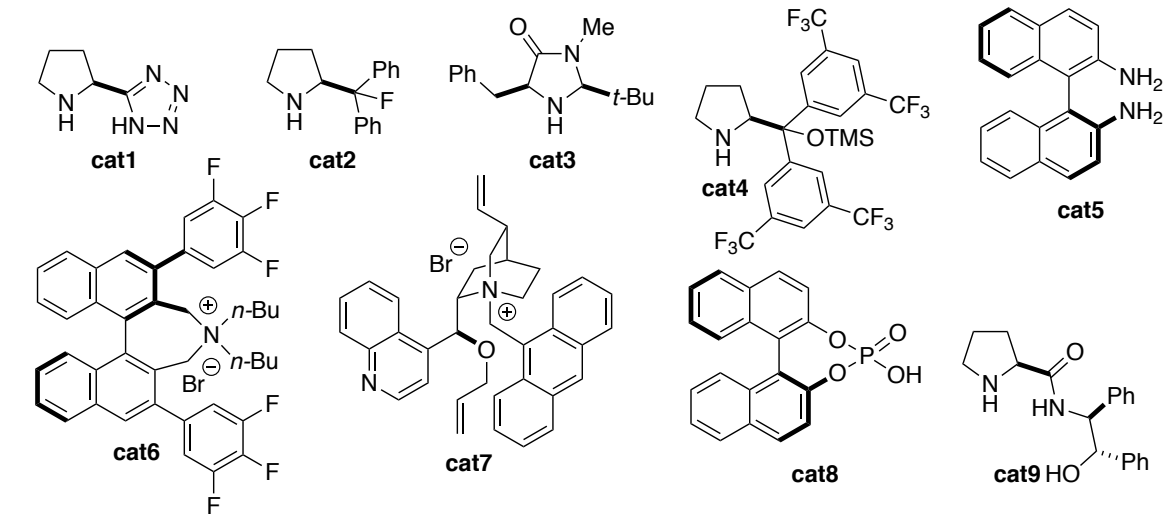
With the proof of principle in hand, the four-fold ozonolysis was examined in more detail. Different solvents and reducing agents were tested, while the aldol condensation was performed with the pyrrolidinyl-tetrazole catalyst **cat1**. Since the yield of the aldol condensation was unknown, it was assumed to be unaffected by the tested reducing agents. Thus, the efficiency of the reducing agent was estimated from the ratio of formed benzaldehyde (cleaved from the olefin in the cinnamyl side chain) and the binaphthalene product **14a** in the crude NMR spectra. None of the tested reducing agents gave comparable results to PPh_3 and only trace amounts of **14a** were obtained with dimethyl sulfide, zinc and acetic acid, dihydrogen and palladium on charcoal, thiourea[107] or NMO.[108] Further examination therefore focused on phosphine reducing agents. After obtaining low yields for the ozonolysis and aldol condensation sequence using PCy_3, PBu_3, $P(OMe)_3$ or 4-(diphenylphosphaneyl)aniline, PPh_3 was selected as our reducing agent of choice and further optimization focused on the influence of solvents, which had to be chosen carefully due to the potential reaction with the highly reactive ozone. The ozonolysis and aldol condensation sequence in DCE, EtOAc and toluene was not as efficient as in dichloromethane, but comparable results were observed with $CHCl_3$.

After the optimization of the ozonolysis conditions, the double arene-forming aldol condensation was examined in detail. The determination of the yield of the ozonolysis step which enables to decouple the ozonolysis step from the aldol condensation would enormously simplify its investigation. Furthermore, the determination of the substrate concentration was crucial for a precise substrate to catalyst ratio. Since the best results for the ozonolysis were obtained with dichloromethane and chloroform, performing the reaction in CD_2Cl_2 and $CDCl_3$ may allow the determination of the yield by NMR with an internal standard. Together with D. Häussinger it was possible to characterize the hexa-carbonyl substrate **13a** by NMR from a PPh_3 free sample. In solution, **13a** exists in at least two tautomeric forms, but the benzylic protons were found to be suitable to determine the yield of the ozonolysis reaction (see Supporting information for more details). The yield of the ozonolysis was in the range of 46-50% if the reaction was performed under diluted conditions, which is remarkably efficient considering that four olefins are cleaved in one step (up to 84% yield per olefin).

As a next step, the double arene-forming aldol condensation was examined in more detail. The investigations were initially focused on the examination of different catalysts in order to optimize the enantioselectivity of the noncanonical polyketide cyclization. At the outset of the optimization of the aldol condensation, a range of different secondary amine and ion-pairing catalysts were investigated. With the possibility to determine the yield of the aldol condensation, the pyrrolidinyl-tetrazole catalyst **cat1** was examined again to have a starting point for the evaluation of other catalysts. A promising yield of 65% and an e.r. of 67:33 was obtained with 80 mol% of **cat1** (Table 3, Entry 1). The utility of secondary amine catalysts was confirmed by the use of L-proline yielding the product **14a** in 50% and an increase in enantioselectivity to 85:15 (Table 3, Entry 2). A poor yield of 9% was observed with the fluorinated proline derivative **cat3** and no product was formed with a MacMillan type catalyst **cat3** and only traces with the Jørgensen-type catalyst **cat4** (Table 3, Entries 3-5). No improvement was achieved with the diamine catalyst **cat5** with a yield of 11% and a moderate enantioselectivity of 68:32 (Table 3, Entry 6). To investigate a different activation mode, two ion-pairing catalysts were examined, however no product formation was observed (Table 3, Entries 7+8). The absence of product formation in the reaction with the chiral phosphoric acid **cat8** underlined the efficiency of secondary amine catalysts for this double arene-forming aldol condensation (Table 3, Entry 9).

Table 3: Investigation of different amine and ion-pairing catalysts for the double arene-forming aldol condensation.[c]





Entry[a]	Catalyst (mol%)	Time [h]	Solvent	Yield [%][b]	e.r.[c]
1	**cat1** (80)	48	$CDCl_3$	65	67:33
2	L-proline (80)	66	$CDCl_3$	50	85:15
3	**cat2** (50)	19	$CDCl_3$	9	-
4	**cat3** (40)	24	CD_2Cl_2	-	-
5	**cat4** (40)	24	CD_2Cl_2	traces	
6	**cat5** (20)	113	$CDCl_3$	11	68:32
7	**cat6** (40)	19	$CDCl_3$/aq. KOH (1M), 5:1	-	
8	**cat7** (40)	19	$CDCl_3$/aq. KOH (1M), 5:1	-	-
9	**cat8** (40)	24	$CDCl_3$/toluene-d_8, 5:1	-	-
10	**cat9** (80)	63	$CDCl_3$	62	95:5

[a] Performed with 10.0 μmol of **13a** in 2.0 mmolL^1; [b] The yield was determined by NMR with an internal standard; [c] The e.r. was determined by HPLC on a chiral stationary phase.

[c] Examination of amine and ion-pairing catalysts was performed together with Dr. Vincent C. Fäseke

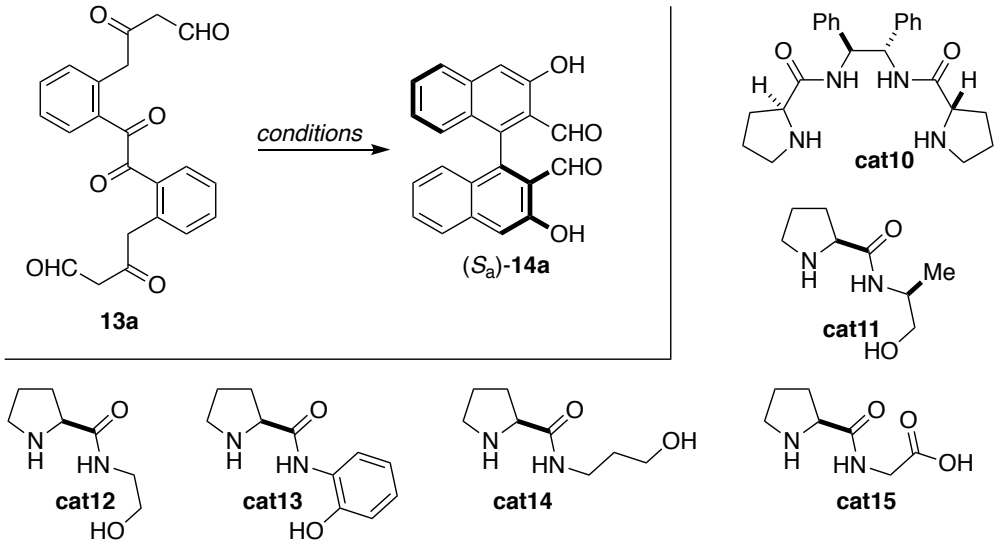
Consequently, more secondary amine catalysts were examined disclosing the excellent performance of the commercially available catalyst **cat9**.[109] The pyrrolidine carboxamide catalyst bearing an additional hydrogen-bond donor in the side chain yielded the product **14a** in a good yield of 65% and a significantly improved enantioselectivity of 95:5. (Table 3, Entry 10).

Good yields were generally found for the double arene-forming aldol condensation by the use of secondary amine catalysts (comprehensive table in the supporting information). However, moderate enantioselectivity was observed with secondary amine catalysts except for catalyst **cat9**. By comparison of the examined catalysts, it became evident that **cat9** is the only secondary amine catalyst bearing an additional hydrogen-bond donor besides the carboxylic acid or the corresponding amide functionality. Therefore, we decided to examine the influence of this additional hydrogen-bond donor in more detail and synthesized a variety of related catalysts.

The bisprolineamide **cat10** was reported being twice as active as catalyst **cat9** in aldol reactions and the enhanced activity was attributed to the additional proline unit.[110] In the double arene-forming aldol condensation, nevertheless, the activity of **cat10** was found to be comparable to the catalyst **cat9**. However, an increase of the yield to 74% was obtained with retaining enantioselectivity of 95:5 (Table 4, Entry 1). While the additional proline unit did not lead to significant improvements, we intended to explore the effect of the substituents on the ethanolamine side chain. Catalyst **cat11** derived from L-alaninol contained only one methyl substituent instead of the two phenyl groups. With a yield of 74% and an enantioselectivity of 94:6, the substitution of the ethanolamine side chain appears to have only little influence on the reaction outcome (Table 4, Entry 2; compared to catalyst **cat9**, Table 3, Entry 10: 62% yield, e.r. = 95:5). Consequently, the further simplified catalyst **cat12**,[111] bearing no substituent on the ethanolamine, was examined and the enantioselectivity was even slightly higher with 96:4 together with a good yield of 65% (Table 4, Entry 3). Reducing the flexibility of the sidechain by replacement of the ethanolamine with an aminophenol moiety did not influence the outcome of the reaction yielding the binaphthalene **14a** in 67% and a high enantioselectivity of 96:4 (Table 4, Entry 4). The proximity of the hydrogen bond donor to the secondary amine was examined with the catalyst **cat14** bearing a propanolamine side chain resulting in a slightly decreased enantioselectivity of 93:7 (Table 4, Entry 5). A more acidic hydrogen-bond donor was investigated with the dipeptide **cat15**, but a drop in enantioselectivity to 91:9 was observed (Table 4, Entry 6). Additionally, the low solubility of **cat15** lead to inconsistent results on larger scales and was therefore not further examined.

The catalyst examination was performed on a small scale of 10.0 µmol of substrate **13a**. Considering a prospective scope examination, the activity of the secondary amine catalysts has to be examined on a larger scale.

Table 4: Investigations of secondary amine catalysts bearing hydrogen-bond donating side chains.[d]



Entry[a]	Cataylst (mol%)	Time [h]	Yield [%][b]	e.r.[c]
1	**cat10** (80)	63	74	95:5
2	**cat11** (80)	63	74	94:6
3	**cat12** (80)	48	65	96:4
4	**cat13** (80)	48	67	96:4
5	**cat14** (80)	64	55	93:7
6	**cat15** (80)	22	72	91:9.
7[d]	**cat12** (80)	**66**	**82**[e]	**95:5**
8[d]	**cat13** (80)	157	70[e]	94:6

[a] Performed on a 10.0 µmol of **13a** in 2.0 mmolL^{1} in $CDCl_3$; [b] The yield was determined by NMR with an internal standard; [c] The e.r. was determined by HPLC on a chiral stationary phase; [d] Performed on a 100 µmol scale; [e] Isolated yields.

Since the highest enantioselectivities were obtained with the catalysts **cat12** and **cat13**[112], they were tested on a 100 µmol scale. Retaining reaction rate was observed for the ethanolamine catalyst **cat12** and an increased yield of 82% with a high enantioselectivity of 95:5 was obtained within 66 hours (Table 4, Entry 7). On the other hand, a decelerated turnover rate was observed for the

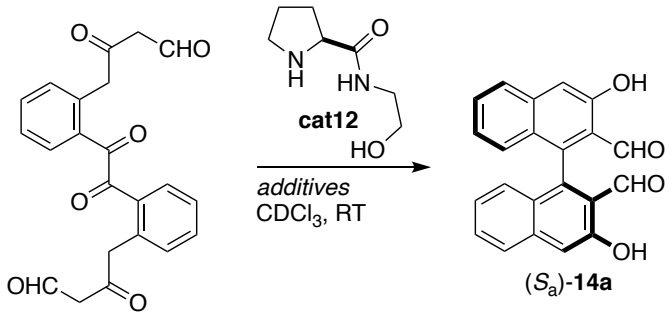
[d] Investigations of secondary amine catalysts bearing hydrogen-bond donating side chains was performed together with Dr. Vincent C. Fäseke.

aminophenol congener **cat13** and a prolonged reaction time of 157 hours was required to isolate the product **14a** in 70% yield (Table 4, Entry 8).

The good yields and high enantioselectivities obtained for every examined catalyst in Table 4 emphasized the importance of additional hydrogen-bond donors of the secondary amine catalysts for the double arene-forming aldol condensation. The low impact of various substituents further underlined these findings and the highest enantioselectivities were observed with the unsubstituted ethanolamine catalyst **cat12**. The additional hydrogen-bond donor possibly forms an extended hydrogen-bond network between the catalyst and the substrate **13a**. The flexible hexa-carbonyl substrate **13a** is thereby preorganized to a well-defined transition state leading to high enantioselectivities. Even though good yields and high enantioselectivities were achieved, the developed method had two limitations. One drawback is the high catalyst loading of 80 mol% which was required to reach consistently high enantioselectivities and good yields. The second shortcoming was the long reaction time. To address these issues, catalyst **cat12** was further investigated in combination with additives.

Looking for possible additives to accelerate our aldol condensation reaction, we found a report from Zhang and co-workers describing a 24-fold acceleration of an organocatalyzed domino Michael addition through the addition of $NaHCO_3$ to the reaction mixture.[113] We therefore examined different inorganic bases to evaluate the applicability to our system. The double arene-forming aldol condensation was rather decelerated than accelerated and after 90 hours reaction time, the binaphthalene **14a** was obtained in poor yields of 16-42% (Table 5, Entries 1-3). On the other hand, good yields were observed with the addition of organic bases such as DABCO and TMEDA. However, the significant drop in enantioselectivity indicated the occurrence of an unselective background reaction (Table 5, Entries 4–5). While basic additives either led to deceleration of the catalytic activity or an undesired background reaction, we turned our focus on the investigation of acidic additives. Equimolar amounts of TFA added to the catalyst solution reduced the reaction time by a factor of three to 24 hours with only a slight loss in enantioselectivity to 92:8 (Table 5, Entry 6). Additionally, the catalyst loading could be decreased by half to 40 mol% (20 mol% per cyclization) providing the binaphthalene dicarbaldehyde **14a** in a good yield of 63% and an e.r. of 87:13 (Table 5, Entry 7).

Table 5: Examinations of additives with catalysts **cat12** to reduce the reaction time and lower the catalyst loading.[e]



Entry[a]	Catalyst (mol%)	Time [h]	Additive (mol%)	Yield [%][b]	e.r.[c]
1	**cat12** (80)	90	$NaHCO_3$	42	n.d.
2	**cat12** (80)	90	$KHCO_3$	28	n.d.
3	**cat12** (80)	90	Na_2CO_3	16	n.d.
4	**cat12** (80)	90	DABCO (200)	63	64:36
5	**cat12** (80)	90	TMEDA (200)	67	65:35
6	**cat12** (80)	24	TFA (80)	76	92:8
7	**cat12** (40)	44	TFA (40)	63	87:13

[a] Performed with 10.0 µmol of **13a** in 2.0 $mmolL^{1}$ in $CDCl_3$; [b] The yield was determined by NMR with an internal standard; [c] The e.r. was determined by HPLC on a chiral stationary phase.

The prolonged reaction time as well as the high catalyst loading were successfully reduced through the addition of TFA. The role of the TFA in the catalytic system is not entirely clear, but we assume that the dehydration step is enhanced and potentially leads to a faster release of the catalyst from the product (Discussed in more detail in section 3.5.). However, to maintain the high enantioselectivity in the developed methodology, we decided to keep the catalyst loading of the ethanolamine catalyst **cat12** at 80 mol%, since it can be effortlessly prepared on large quantities in a two-step procedure.

3.3.1. Synthesis of Symmetric Biindenes

With the optimized reaction conditions in hand, the investigation of scope and limitations of the double arene-forming aldol condensation was initiated with the preparation of substituted biindenes. A multitude of binaphthalene ligands is derived from BINOL and thus modifications of

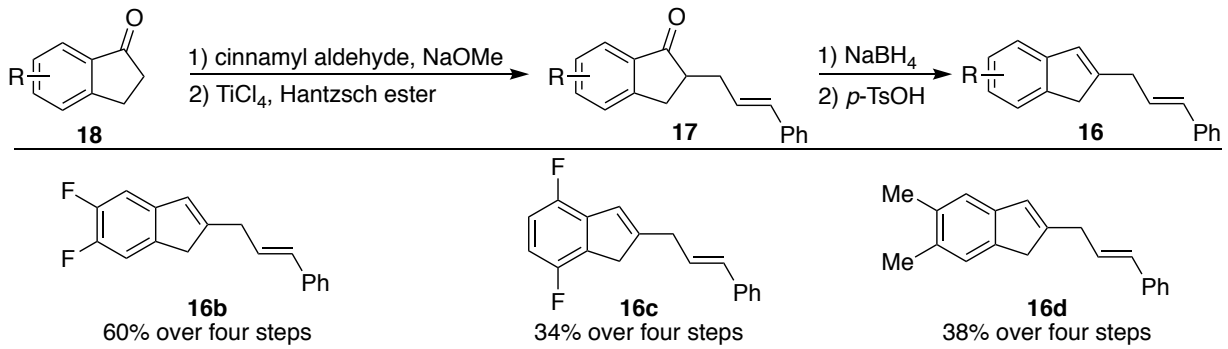
[e] Examination of additives was performed together with Dr. Vincent C. Fäseke.

the ligand backbone is mostly limited to the introduction of 3,3'-substituents (section 1.3.1) or partial hydrogenation of the binaphthalene.[114] Considering potential application of our biaryl products as ligands for catalysis, we intended to prepare binaphthalene scaffolds, which were previously difficult to access. Fluorinated binaphthalene scaffolds are of great interest in catalyst design[115] and consequently, we initiated the preparation of substituted precursors by the synthesis of fluorinated biindenes. For the synthesis of symmetric biindenes, we planned to utilize the same synthetic strategy as for the preparation of the biindene **15a**.

The aldol condensation of the electron-deficient 5,6-difluoroindanone **18b**[116] and cinnamyl aldehyde was much slower compared to 1-indanone **18a**, but with elevated temperatures of 70 °C, the aldol condensation product was obtained in a good yield of 74% yield. In the 1,4-reduction of the 5,6-difluoro indenone, an excellent yield of 91% was achieved with a solvent switch from THF to dichloromethane. The difluoro indanone **17b** was reduced with sodium borohydride and subsequently dehydrated under acidic conditions using *p*-TsOH. The difluoro indene monomer **16b** was obtained in 90% yield in this two-step sequence resulting an an excellent overall yield of 60% over four steps (Scheme 43).

The 4,7-difluoroindanone **18c**[117] was even less reactive than the 5,6-difluoroindanone **18b** and required a temperature of 76 °C for the aldol condensation step. Increasing the amount of sodium methoxide led to side reactions rather than an acceleration of the reaction. The following 1,4-reduction gave the best results in THF yielding the 4,7-difluoroindanone **17b** in 67%. The reduction with $NaBH_4$ was quantitative, but the dehydration step was found to be slow and an extended reaction time of 96 hours was required to yield the 4,7-difluoro indene **16c** in 89% over two steps (Scheme 43).

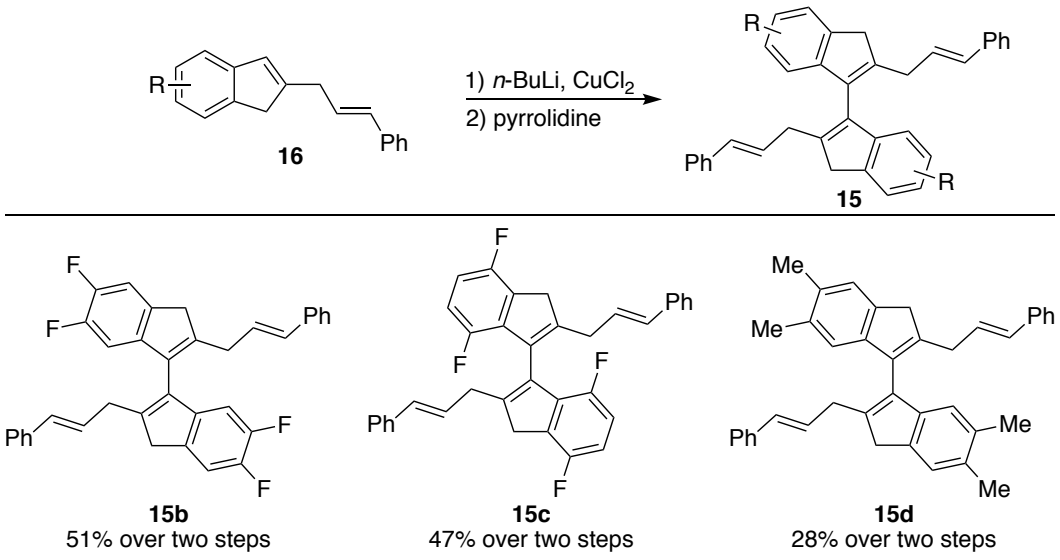
The aldol condensation with the electron-rich 5,6-dimethylindanone **18d** was performed at room temperature and the 5,6-dimethyl indenone was isolated in 80% yield. The 1,4-reduction with the 5,6-dimethyl indenone was not as selective as for electron-deficient substrates and 18% of 1,6-reduction product was obtained, which could be separated on the subsequent reduction and elimination steps yielding the 5,6-dimethyl indene **16d** in an overall yield of 38% over four steps (Scheme 43).



Scheme 43: Synthesis of indenes **16b-d.**

The developed four-step procedure for the preparation of the indene monomers was generally applicable and enabled the efficient preparation of two electron-deficient as well as one electron rich indene monomer. For the final preparation of biindene precursors, the oxidative dimerization and olefin isomerization sequence was tested with the prepared indenes **16b-d**.

The 5,6-difluoro indene **16b** was converted into the biindene **15b** under identical conditions as for the unsubstituted biindene **15a** with *n*-BuLi and copper chloride followed by the olefin isomerization. A still useful yield of 51% was obtained over the two steps, indicating the general applicability of this dimerization process. A similar outcome was observed for the electron-deficient 4,7-difluoroindene **16c** yielding the tetrafluoro biindene **15c** in a slightly lower yield of 47%. The increased steric demand of the fluoride substituents in *peri*-position thereby marginally affected the reaction outcome. However, the electron-rich 5,6-dimethylindene **16d** was more challenging to dimerize, giving a moderate yield of 28% over two steps (Scheme 44).

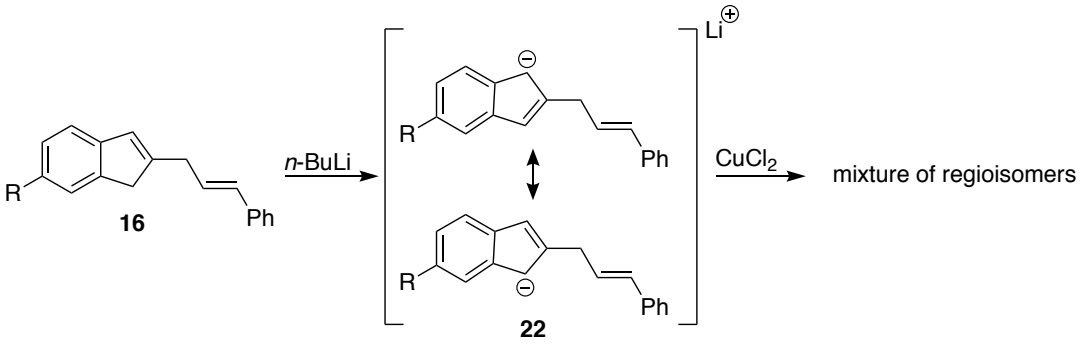


Scheme 44: Oxidative dimerization and olefin isomerization of the symmetric indenes **16b-d**.

The preparation of three symmetric biindenes **15b-d** demonstrated the utility of the oxidative dimerization and olefin isomerization sequence to prepare the precursors for the four-fold ozonolysis and subsequent double arene-forming aldol condensation.

3.3.2. Symmetric Precursors from Mono-substituted Indenes

To further extend the variety of symmetric precursors, the oxidative dimerization of mono-substituted indenes was investigated. The required monomers were prepared with the same reaction sequence as for the disubstituted indenes (section 3.3.1). However, the oxidative dimerization was found to be a critical step due to regioselectivity issues with unsymmetric indenes. After deprotonation of the unsymmetric indene with *n*-BuLi, the allyl anion **22** is in a rapid equilibrium which results in a complex mixture of inseparable regioisomers in the copper-based dimerization process (Scheme 45).



Scheme 45: Resonance forms of cinnamyl indenyl anion **22** leading to a mixture regioisomers in the oxidative dimerization.

A different strategy than the oxidative dimerization would be necessary to ensure a selective coupling of mono-substituted indenes. However, considering the development of an alternative precursor synthesis, the preparation of unsymmetric precursors would be even more useful.

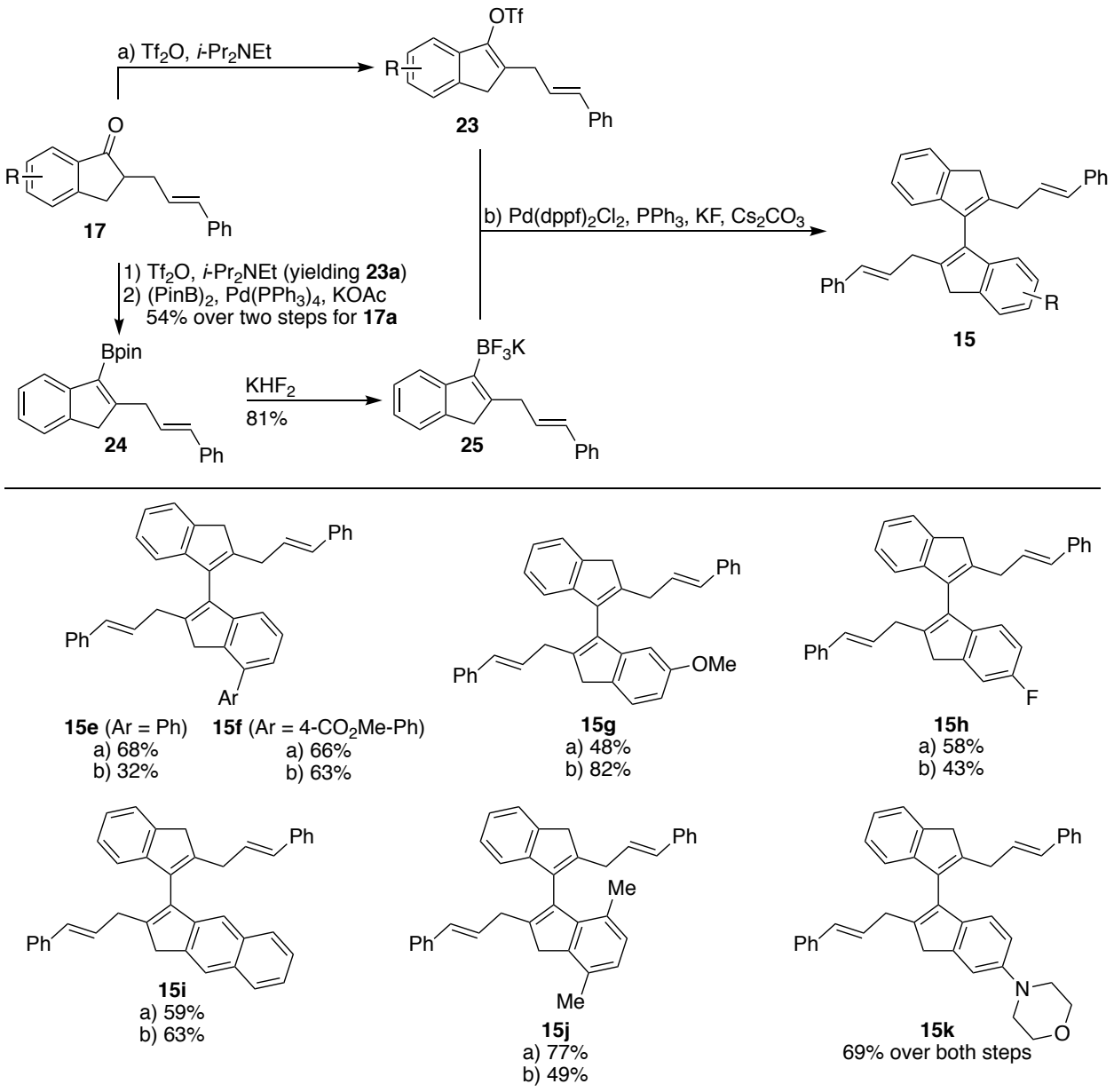
3.3.3. Synthesis of Unsymmetric Biindenes

Expanding the scope of the double arene-forming aldol condensation for the stereoselective preparation of unsymmetric binaphthalene dicarbaldehydes would be particularly valuable since most complementary oxidative dimerization processes are limited to symmetric binaphthyl scaffolds.[60] We thus anticipated a cross-coupling reaction as one of the most versatile methods for carbon-carbon bond formation as a suitable alternative to the oxidative dimerization. Thereby, conversion of indanones into the corresponding enol triflates would readily deliver a pseudo halide

for the coupling reaction. The organometallic coupling partner was first planned to be accessed *in situ* from the deprotonated cinnamyl indene **16a** via a transmetallation with (*i*-PrO)Bpin or zinc chloride at low temperature but this was found to be challenging and no conversion in the coupling reaction was observed. We therefore aimed for the preparation and isolation of an organometallic coupling partner to reduce the complexity of the cross-coupling reaction. The synthesis of an indenyl borane compound through a Miyaura borylation appeared as most promising strategy.

Exploration of the intended cross-coupling strategy was initiated with the synthesis of indenyl triflates from the corresponding indanones. A generally applicable procedure was found with *i*-$PrNEt_2$ as a base in combination with triflic anhydride, which enabled the preparation of enol triflates **23e-k** in 48-77% yield. Poor yields were obtained with alternative methods such as LDA and phenyl triflimide. Some indanones required adjusted reaction conditions as for example the preparation of enol triflate **23f**. A change of the base to 2,6-di-*tert*-butylpyridine was necessary to prevent undesired polymerization reactions. Furthermore, the enol triflate prepared from the morpholino indanone was found being unstable and had to be converted immediately after purification.

The unsubstituted indenyl triflate **23a** was prepared on a 100 mmol scale for further conversion into an organoborane compound as coupling partner for the prepared enol triflates. A Miyaura borylation[118] was found to be a convenient protocol for the conversion of the triflate **23a** boronic pinacol ester **24**. With the enol triflates **23e-k** and the boronic pinacol ester **24** in hand, the Suzuki cross-coupling reaction was investigated in detail. After thorough examination of different coupling conditions, a combination of $Pd(dppf)_2Cl_2$ as catalyst, PPh_3 and a combination with Cs_2CO_3 and KF lead to the desired coupling product. Protodeboronation was the major side reaction and just the two aryl-substituted indenyl triflates **23e+f** could be converted into the corresponding unsymmetric biindenes **15e+f** in acceptable yields of 32% and 63%. As a strategy to prevent the undesired protodeboronation,[119] the trifluoroborate salt **25** was synthesized from the pinacol ester **24** with KHF_2 in a good yield of 81%. Under the same coupling conditions and the use of the trifluoroborate salt **25**, the unsymmetric biindenes were prepared from enol triflates **23g-k** in yields between 43% and 82% (Scheme 46). The indenyl triflate of the 4-cyano indanone could not be prepared in synthetically useful yields with this method and in the following cross-coupling reaction, no biindene formation was observed for this substrate.

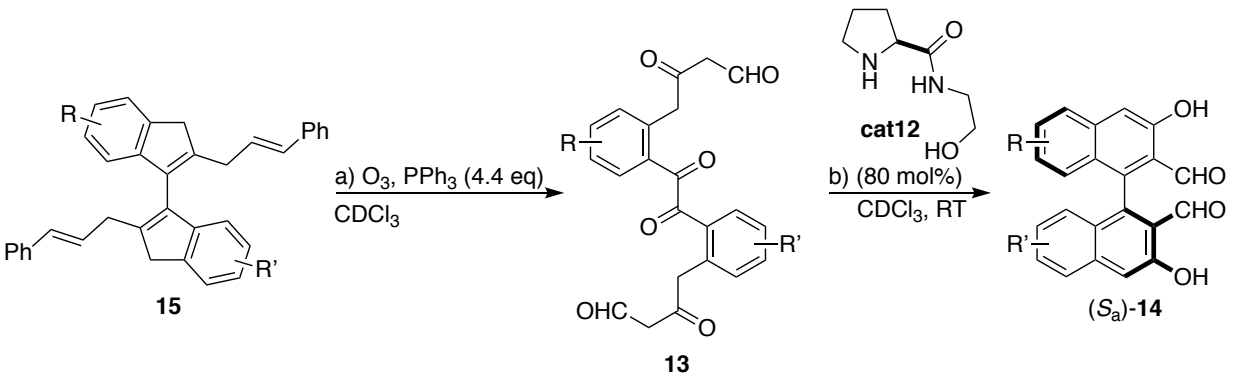


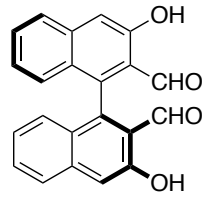
Scheme 46: Synthesis of unsymmetric biindenes **15e-k** through a Suzuki cross-coupling of indenyl triflates **23e-k** and the trifluoroborate salt **25**.

In addition to the three symmetric biindenes **15b-d**, the developed Suzuki cross-coupling reaction of indenyl triflates and indenyl boranes enabled the preparation of seven unsymmetrically substituted biindenes. Thus, we were excited to explore the four-fold ozonolysis and the double arene-forming aldol condensation to evaluate the scope and limitations of our protocol for the atroposelective synthesis of tetra-*ortho*-substituted biaryls.

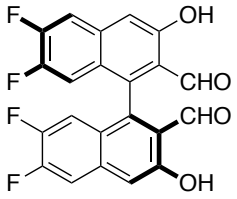
3.4. Scope of the Noncanonical Polyketide Cyclization

Initially, the reaction scale with the model substrate **13a** was further increased to a 1.00 mmol scale confirming that the tetra-*ortho*-substituted binaphthalenes are accessible in high yields and excellent selectivity (1.00 mmol: 76%, e.r. = 96:4, 100 µmol: 82%, e.r. = 95:5). With the symmetric and unsymmetric biindene precursors in hand, we next examined the scope and limitations of the double arene-forming aldol condensation using 80 mol% of catalyst **cat12** in $CDCl_3$ at room temperature. We were delighted to find that the electron deficient tetra-fluorinated hexacarbonyl substrate **13b** was obtained in 58% yield in the ozonolysis and the following cyclization yielded the binaphthalene **14b** in 60% yield and an e.r. of 92:8 underlining the versatility of the method. With the hexa-carbonyl substrate **13c**, obtained in 30% yield from the ozonolysis of **15c**, the boundaries of steric interactions for the aldol condensation were tested. The di-*peri*-substituted binaphthalene **14c** was obtained in an excellent e.r. of 98:2 albeit in a low yield of 24%. However, this is to the best of our knowledge the first example for the stereoselective preparation of a *peri*-substituted binaphthalene. Regarding the accessibility of unsymmeric binaphthalene products, a phenyl substituent in the 5-position enabled the preparation of a terphenyl system **14e** in 60% yield and an e.r. of 91:9. This finding was further pursued and the phenyl moiety was changed to a methyl benzoate as a potential anchoring group for catalyst immobilization.[120] The methyl benzoate substrate **13f** was accessible in 48% yield in the ozonolysis and the cyclization efficiently provided the binaphthalene **14f** in a high yield of 80% and an e.r. of 90:10. For this substrate, the enantioselectivity was affected by the scale of the reaction since an excellent e.r. of 98:2 was only obtained on a reduced scale. The effect of an electron-donating group was examined with the methoxy-substrate **13g**. Thereby, the addition of TFA was beneficial in order to reach completion of the reaction and **14g** was isolated in an excellent yield of 93% although the enantioselectivity was slightly lower with 90:10 compared to the electron deficient products. The mono-fluoro substrate **13h** was obtained in a good yield of 53% from ozonolysis and the addition of TFA was again advantageous for the aldol condensation step which efficiently provided the binaphthalene **14h** in a good 85% yield and a high e.r. of 94:6 (Scheme 47).

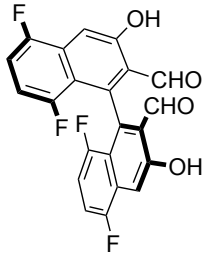




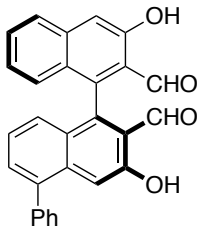
14a
a) 49% yield
b) 100 μmol scale: 82% yield, 95:5 e.r.
1.00 mmol scale: 76%, 96:4 e.r.



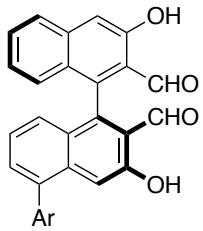
14b
a) 59% yield
b) 61% yield, 92:8 e.r.



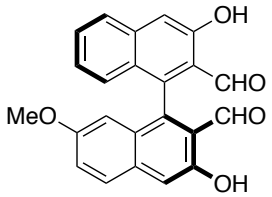
14c
a) 30% yield
b) 24% yield, 98:2 e.r.



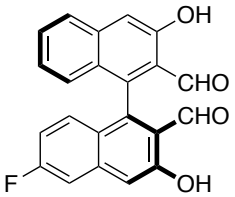
14e
a) 38% yield
b) 60% yield, 91:9 e.r.



14f (Ar = Ph-4-CO_2Me)
a) 48% yield
b) 80% yield, 90:10 e.r.
10 μmol scale: 98:2 e.r.



14g[a]
a) 37% yield
b) 93% yield, 90:10 e.r.



14h[a]
a) 53% yield
b) 85% yield, 94:6 e.r.

Scheme 47: Scope of the noncanonical polyketide cyclization. The reactions were performed with 50.0 μmol of substrates **13** in $CDCl_3$ at a concentration of 2.00 mmolL^{-1} at RT and 40.0 μmol of catalyst **cat12**; [a] Addition of 80 mol% of TFA.

The combination of a four-fold ozonolysis proved being an efficient synthetic strategy to access different hexa-carbonyl substrates. The secondary amine catalyst **cat12** triggered a stereoselective double arene-forming aldol condensation which enabled to access a variety of symmetric and unsymmetric substituted tetra-*ortho*-substituted binaphthalenes in good yields and high atroposelectivites including the first atroposelective synthesis of a di-*peri*-substituted binaphthalene.

3.4.1. Limitations

During the scope examination, a number of limitations of the developed methodology were identified. The high reactivity of the ozone was problematic for some biindenes through the occurrence of undesired side reactions. For instance, the ozonolysis of the electron-rich tetra-methyl biindene **15d** yielded an unknown compound which did not react under the conditions for the aldol condensation. The absence of the benzyl groups indicated a possible reaction of the ozone with the electron-rich arenes. Basic amine functionalities were also not compatible with the ozonolysis conditions and the hexa-carbonyl substrates of the unsymmetric biindenes **15k** and **15l** were not accessible. The ozonolysis reaction turned black while warming up to room temperature and NMR analysis of the reaction mixture indicated the formation of substantial amounts of polymerization products. Initiation of these undesired side reactions is probably the competing oxidation of the basic nitrogen by ozone. Suppression of these oxidations was not sufficiently reduced by protonation of the nitrogen, neither with a solvent switch to MeCN[121] or through the protection of the morpholine as the N-oxide (Figure 14, a.).[122]

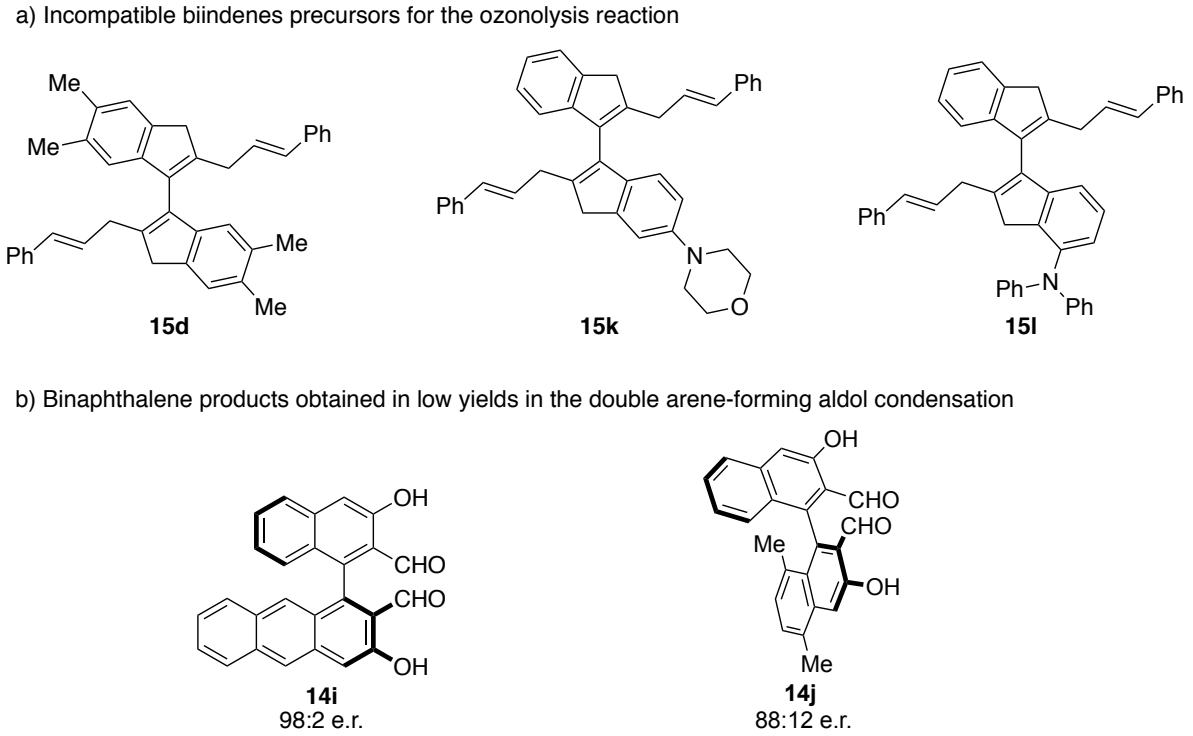


Figure 14: a) Biindenes which could not be converted into the corresponding hexa-carbonyl substrates due to side reactions with ozone; b) The binaphthalenes **14i** and **14j** were only obtained in low yields in the double arene-forming aldol condensation.

Low yields were obtained in the ozonolysis of biindene **15i**, but the examination of the aldol condensation was possible. The anthracene **14i** was obtained in an excellent atroposelectivity of 98:2, however only in low yields. Again, a competing side reaction of the ozone with the aryl backbone might be the reason for the poor yields. Similarly, low yields were obtained for the binaphthalene **14j**, but small amounts of product were isolated and an e.r. of 82:18 was determined. (Figure 14, b.).

The main limitations of the reaction sequence are attributed to the ozonolysis rather than the aldol condensation step. In contrast to the remarkable one step installation of all carbonyl functions enabled by the ozonolysis reaction, the high reactivity of ozone is critical for functional groups which can be oxidized. Thus, a careful evaluation of intended substrates concerning compatibility with ozone is crucial.

3.4.2. Absolute Configuration and Configurational Stability of the Products

The absolute configuration of the binaphthalene products was determined by X-ray crystallographic analysis of **14a**, **14c** and **14g**. Thereby, the catalyst (*S*)-**cat12** was found to consistently provide (S_a)-configured products **14**. The torsion angles are between 92°– 100° and the aldehydes groups are situated *synperiplanar* to the hydroxy functions in the 3-positions to form an intramolecular hydrogen bond. (Figure 15).

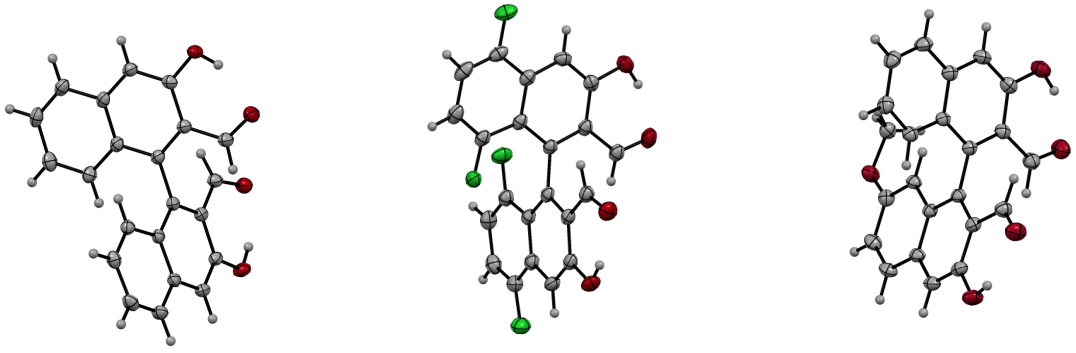
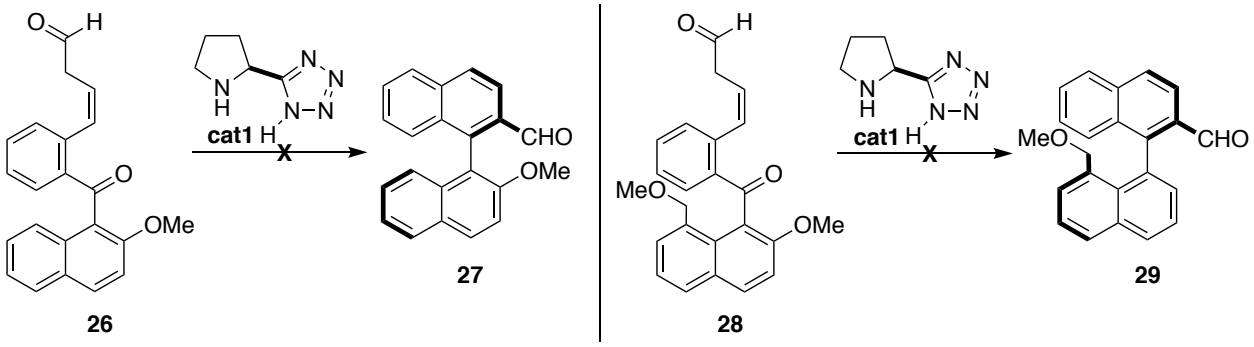


Figure 15: X-ray structures of binaphthalenes **14a** (reflection shown), **14c** and **14g** revealing that (*S*)-**cat12** provides (S_a)-configured products.

Furthermore, atropisomerization studies of binaphthalene dicarbaldehyde **14a** confirmed the characteristically high configurational stability of tetra-*ortho*-substituted biaryls and an exceptionally high stability of $\Delta G^{\ddagger}_{433\ K}$ of more than 150 kJmol[1] was observed even at 160 °C (faster thermal decomposition than racemization).

3.5. Mechanistic Considerations

Different from the previous arene-forming aldol methodology developed in our group, the double arene-forming aldol condensation enabled the preparation of tetra-*ortho*-substituted binaphthalenes and even *peri*-substituents were tolerated. These sterically demanding substrates (**26** + **28**) previously represented a limitation of the initial arene-forming aldol condensation (Scheme 48).[69]



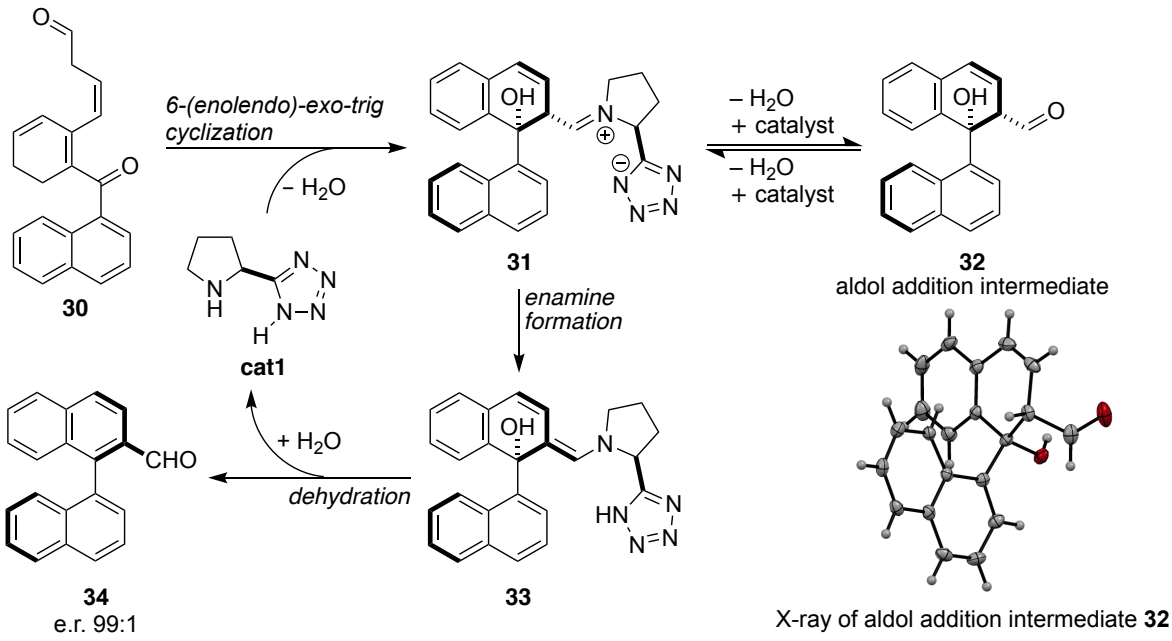
Scheme 48: Limitations of the arene-forming aldol condensation.

Investigations of mechanistic features of the double arene-forming aldol condensation potentially reveal the key differences in the catalytic cycles of these two reactions, which allowed to access the sterically demanding tetra-*ortho*-substituted binaphthalene products. Thereby, we could profit from detailed insights into the mechanism of the arene-forming aldol condensation, which was the main topic in the author's Master studies.

3.5.1. Mechanistic Studies of the Arene-forming Aldol Condensation

The mechanistic studies of the arene-forming aldol condensation were conducted on the basis of the isolation and characterization of the aldol addition intermediate **32**. Especially important was thereby the determination of the absolute configuration of the aldol addition intermediate **32** by X-ray analysis. The isolation of this intermediate allowed an independent investigation of the aldol addition and the subsequent dehydration step. The aldol addition was found to be the stereo-determining step and no difference in enantioselectivity was observed whether the dehydration was performed in presence of the tetrazole catalyst **cat1** or with silica gel. The rate-determining dehydration step was enhanced in the presence of the catalyst **cat1**, thus having a dual role in the catalytic system. From these insights, a catalytic cycle was proposed which starts with the condensation of the catalyst **cat1** with the aldehyde of the substrate **30**. Enamine formation triggers

the aldol addition resulting in a quaternary ammonium-ion **31**, that either tautomerizes into the more stable enamine **33** or is hydrolyzed to the aldol addition intermediate **32** which was fully characterized. X-ray analysis revealed a *syn*-conformation of the aldehyde and the hydroxy function. If not hydrolyzed, the enamine **33** proceeds in the catalytic cycle with a catalyst promoted dehydration leading to the aromatization of the newly formed six-membered ring. Subsequent hydrolysis releases the catalyst **cat1** and the binaphthalene carbaldehyde product **34** (Scheme 49).[123]



Scheme 49: Proposed catalytic cycle from the mechanistic insights of the arene-forming aldol condensation.

Additionally, secondary amine catalyst without a hydrogen-bond donor resulted in olefin isomerization of the substrate rather than product formation, as a first indication for the importance of the hydrogen-bonding abilities of the catalyst. This notion was further confirmed through inhibition of the hydrogen-bonding abilities of the catalyst **cat1** through methylation of the tetrazole unit which caused a significant loss of enantioselectivity to 70:30.

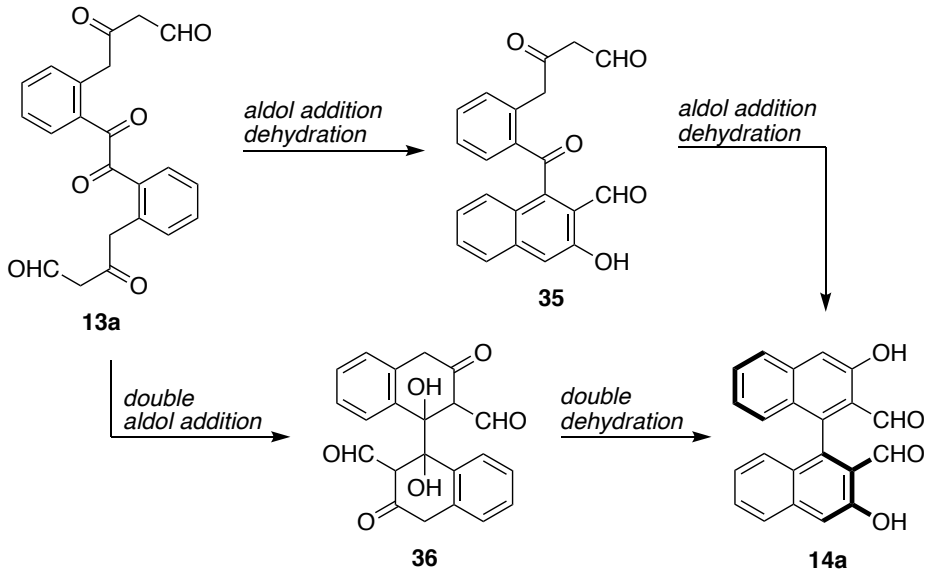
However, it remained elusive whether the aldol addition intermediate **32** already contains a rotationally restricted Csp^2-Csp^3 axis and the dehydration step is not affecting the stereogenic axis. On the other hand, it is possible that the naphthalene unit is still able to rotate but the dehydration only occurs stereospecifically in a certain orientation of the naphthalene ring. The uniform

conformation observed in the X-ray analysis would thereby be due to higher thermodynamic stability of this intermediate or a crystal structure packing effect.

3.5.2. Mechanistic Studies of the Noncanonical Polyketide Cyclization

The noncanonical polyketide cyclization potentially proceeds through two sequential arene-forming aldol condensations. However, the examination of the scope of the arene-forming aldol condensation has shown the sensitivity of the aldol reaction towards substituents in the 2-position of the naphthalene ring. The first aldol condensation of the hexa-carbonyl substrate **13a** would also result in a keto aldehyde **35** bearing a 2-substituted naphthalene exhibiting a sterically demanding substrate for the second aldol condensation and therefore appears as unfavorable.

The mechanistic studies of the arene-forming aldol condensation revealed that dehydration is the rate-limiting step leading to an accumulation of the aldol addition intermediate. Considering this observation in combination with the sensitivity of the reaction to high steric demand, the noncanonical polyketide cyclization particularly proceeds through a two-fold aldol addition to the intermediate **36** followed by a double dehydration. Thereby, the sterically demanding tetra-*ortho*-substituted binaphthalene **14a** is formed at the end of the catalytic cycle and does not interfere with the second cyclization reaction (Scheme 50).



Scheme 50: Two possible reaction pathways for the noncanonical polyketide cyclization: The reaction undergoes two sequential aldol addition dehydration steps or a double aldol addition to **36** is followed by a double dehydration.

To gain insights into the mechanism of the noncanonical polyketide cyclization, the reaction was performed with the model substrate **13a** and followed by NMR. The consumption of the substrate **13a** (C*H*O of tautomers at 9.65–9.90 ppm) was almost completed within the first hour and a reaction intermediate (signal at 10.13) was accumulated. The intermediate disappeared again completely within 16 hours. In parallel, the product **14a** (ArC*H*O at 9.54 ppm and ArO*H* at 11.03) was constantly enriched over the course of the reaction (Figure 16).

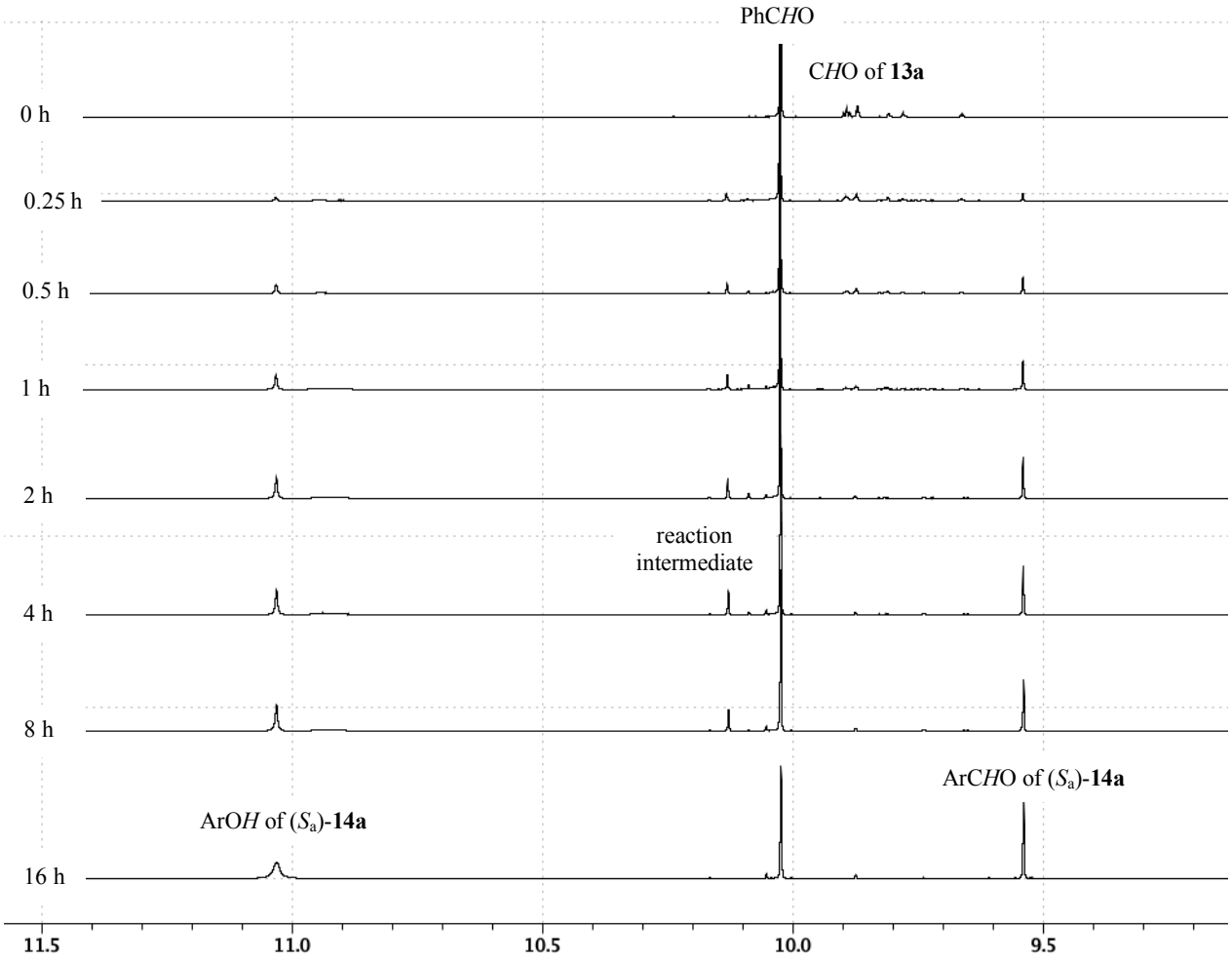


Figure 16: In situ NMR to follow the reaction progress of the noncanonical polyketide cyclization. A reaction intermediate was observed at 10.13 ppm besides the substrate **13a** (C*H*O in tautomeric forms in the range of 9.65–9.90 ppm), benzaldehyde (PhC*H*O at 10.03 ppm) and the product **14a** (ArC*H*O at 9.54 ppm and ArO*H* at 11.03).

The occurrence of only one aldehyde signal from the intermediate (at 10.13 ppm) is indicative for a symmetric molecule, where the two aldehydes are chemically identical. This observation supports the hypothesis of a two-fold aldol addition followed by the double dehydration, since different chemical shifts would be obtained for the naphthaldehyde and the β-ketoaldehyde resulting from a

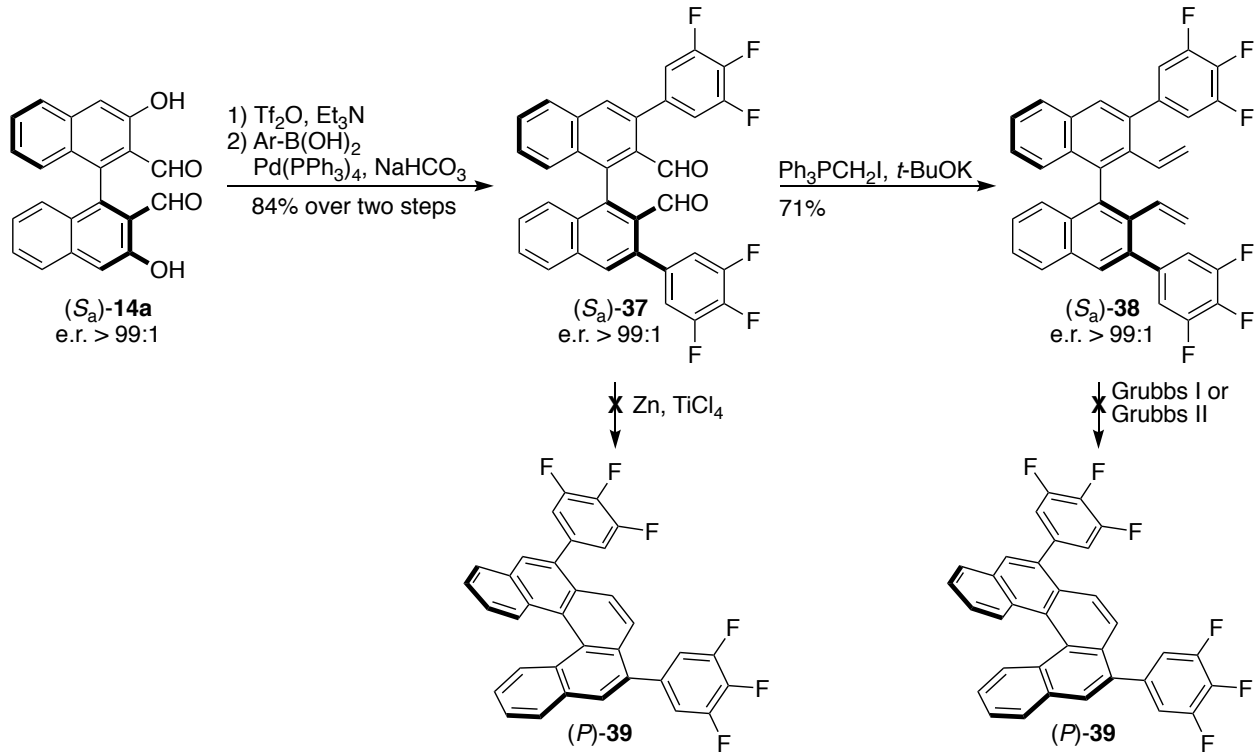
one-fold arene-forming aldol condensation. Further evidence for the formation of a two-fold aldol addition intermediate was obtained by investigating the influence of TFA on the reaction outcome. A rapid disappearance of the signal at 10.13 ppm together with an increase in product formation was observed after the addition of TFA, which is presumably accelerating the dehydration step. However, only for the binaphthalene products **14g** and **14h** the e.r. was not decreased in presence of TFA. A competing unselective side reaction was probably the reason for the lower selectivity observed for the other binaphthalene products. Due to the high steric demand of the Csp^3-Csp^3 single bond of the double aldol addition intermediate, it appears as likely that a rotationally restricted compound is already formed in the aldol addition step and two following dehydrations do not influence the configuration of the axis.

Based on the scope limitations and the mechanistic studies of the arene-forming aldol condensation, a two-fold aldol addition followed by a double dehydration sequence was hypothesized as a plausible mechanism for the noncanonical polyketide cyclization. NMR investigations supported this notion by the appearance of a symmetrical intermediate which might be the double aldol addition intermediate. However, further investigations, as for example the isolation and characterization of this intermediate, are necessary for a conclusive mechanistic model.

3.6. Synthesis of an Atropisomeric Ligand, a [5]Helicene and the Maruoka Catalyst

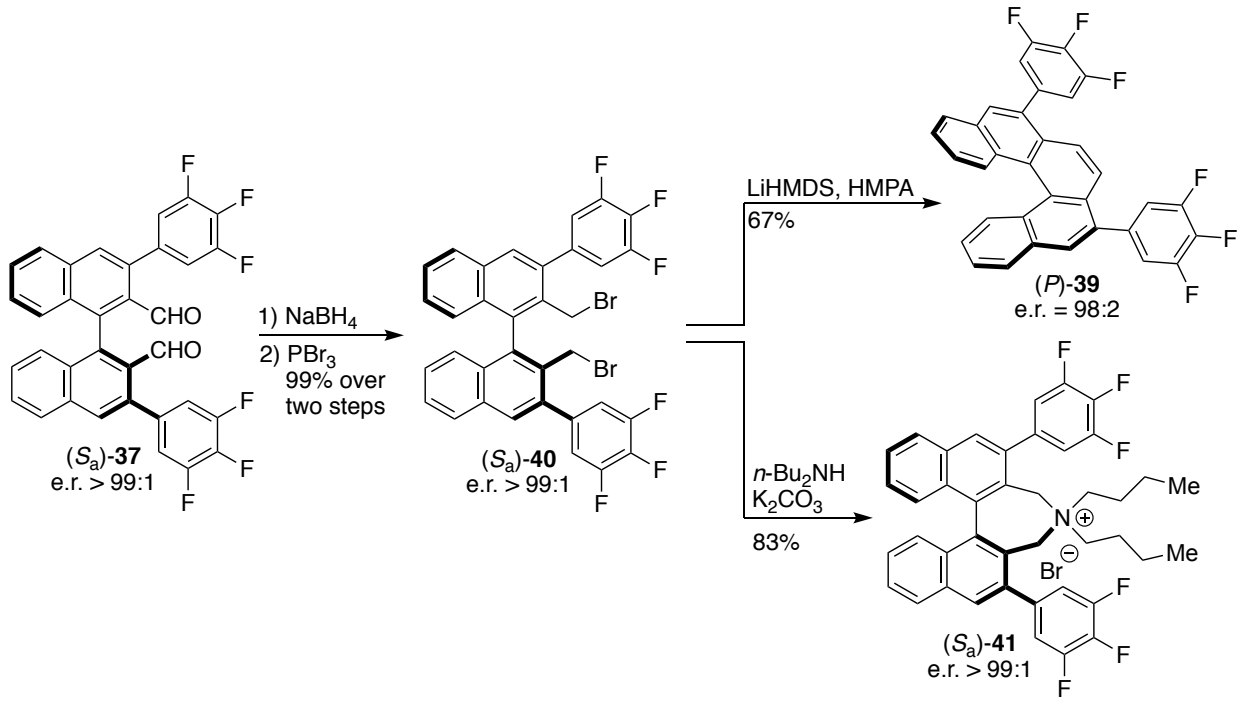
To demonstrate the utility of the tetra-*ortho*-substituted biaryls prepared through the developed methodology, transformations of the binaphthalene scaffold into highly valuable compounds such as ligands, catalysts or even [5]helicenes was explored. The binaphthalene **14a** was therefore recrystallized to achieve an enantiomeric ratio of > 99:1. For the modification of the 3,3'-hydroxy functions, a procedure developed by Maruoka and co-workers was examined first.[44] After triflation with triethylamine and triflic anhydride, the Suzuki cross-coupling reaction was performed with a trifluoro aryl boronic acid and palladium acetate in THF at 65 °C yielding the 3,3'-diaryl binaphthalene **37** in a good yield of 76%. Different to the diester binaphthalene substrate described by Maruoka and co-workers, where no loss in selectivity was described, a drop in the e.r. to 97:3 was observed for the binaphthalene dicarbaldehyde **37**. Thus, more mild coupling conditions were examined. Complete suppression of the racemization was not achieved, but the best results were obtained with $Pd(PPh_3)_4$ and $NaHCO_3$ at room temperature yielding the

binaphthalene **37** in an increased yield of 94% and an e.r. of 98:2. Recrystallization afforded the binaphthalene **37** again in an e.r. of >99:1 with an overall yield of 84%. The dicarbaldehyde **37** was efficiently converted with a double Wittig olefination into the diene **38**, which belongs to a class of diene ligands being used for borane[124] and rhodium catalysis.[125] Ring closing metathesis[126] of the diene **38** would furthermore lead to the preparation of a [5]helicene **39**, a class of compounds particularly interesting as sensors, responsive switches as well as ligand scaffolds in catalysis.[127–128] The ring closing reaction was examined with Grubbs I and Grubbs II catalysts but the diene **38** was unreactive and no conversion was observed. The low reactivity of the substrate **38** might result from the shielding of the dienes through the aryl groups in the 3-positions. A reasonable alternative to the ring closing metathesis would be an intramolecular McMurry coupling, which was described as an efficient method for the conversion of aryl dicarbaldehydes into fused benzenes.[129] The reaction with the dicarbaldehyde **37** was examined according to the literature using zinc and titanium tetrachloride, but no conversion was observed at room temperature. Slow conversion of the substrate **37** was achieved at elevated temperatures, but a mixture of various products was obtained (Scheme 51).



Scheme 51: Preparation of the diene ligand **38** through a triflation and Suzuki cross-coupling sequence followed by a double Wittig reaction. The [5]helicene **39** could not be prepared through a ring closing metathesis nor through a McMurry coupling.

Considering the low configurational stability of [5]helicenes, we turned our attention on methods requiring lower reaction temperatures to reduce racemization during the reaction to a minimum. Gingras and his co-worker described a carbenoid coupling of 2,2'-bis(bromomethyl)-binaphthalene to prepare [5]helicenes at low temperatures.[130] The required dibromide **40** was efficiently synthesized through a reduction of the dicarbaldehyde **37** with sodium borohydride followed by a dibromination with PBr_3 in an excellent yield of 99%. No erosion of the enantiomeric ratio was observed during this two-step procedure. Slightly modified conditions of the carbenoid coupling provided the [5]helicene **39** in a good yield of 67%. Almost complete preservation of the enantiomeric ratio with 98:2 was attained and a remarkable configurational stability of $\Delta G^{\ddagger}_{333\ K} = 109\ \mathrm{kJmol^{-1}}$ was determined for the novel 3,3'-substituted [5]helicene **39**.[f]



Scheme 52: Preparation of the dibromide **40** from dicarbaldehyde **37** through reduction and dibromination. Further conversion of the dibromide **40** into the [5]helicene **39** and the Maruoka catalyst **41**.

Furthermore, the preparation of the dibromide **40** rendered the possibility to access the versatile Maruoka catalyst **41**, which is an outstanding catalyst for ion-pairing catalysis. A two-fold substitution with dibutyl amine yielded the quaternary ammonium salt **41** in a high yield of 83%. With the possibility to access the dibromide **40**, our developed methodology provides an alternative

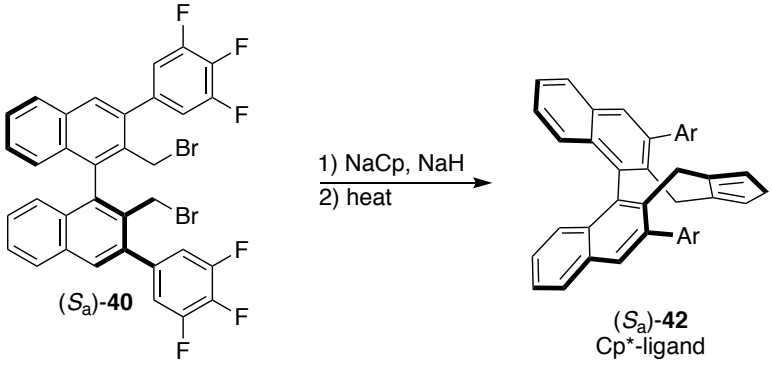
[f] The [5]helicene was synthesized by Dr. Vincent C. Fäseke.

strategy to the previous method starting from either (*S*)- or (*R*)-BINOL and involving numerous steps including a double directed *ortho*-lithiation for the 3,3-substitution of the binaphthalene core and cumbersome protecting group manipulations (section 1.3.1). As an additional advantage of the double arene-forming aldol condensation, the configuration of the binaphthyl core can be controlled by the catalyst at a late stage of the synthesis (Scheme 52).[44,47,51]

The binaphthalene dicarbaldehyde **14a** obtained from the developed double arene-forming aldol condensation was efficiently converted into a chiral diene ligand **38**, a novel 3,3'-substituted [5]helicene **39** and the Maruoka catalyst **41**. The ability to access these three important compounds in the field of sensors and catalysis demonstrated the utility of the binaphthalene products, which are obtained from the developed aldol condensation and accordingly emphasizes the significance of the developed methodology.

3.6.1. Other Potential Applications

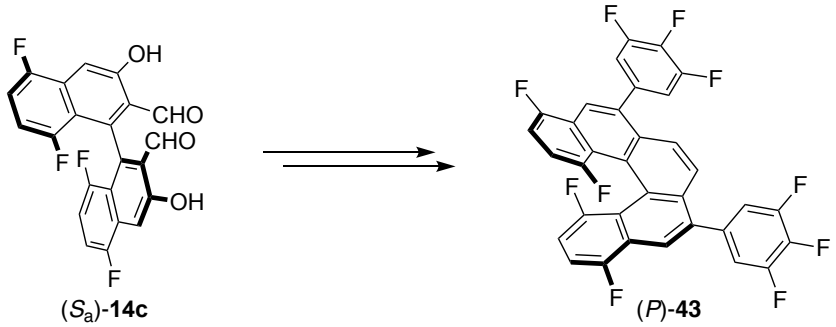
In addition to the [5]helicene **39** and the Maruoka catalyst **41**, the dibromide **40** is moreover a synthetic intermediate for the preparation of chiral cyclopentadienyl ligands **42** (Cp-ligands), useful for transition metal catalysis as discussed in section 1.3.1.[45] Similar to the preparation of the Maruoka catalyst, our synthesis of the dibromide **40** could provide an alternative strategy for the preparation of the chiral Cp*-ligands **42** developed by the Cramer group (Scheme 53).



Scheme 53: Dibromide **40** as a precursor for the preparation of a chiral Cp-ligand **42**.

The possibility to prepare substituted binaphthalene scaffolds could enable the access to new derivates of the prepared ligand, [5]helicene and catalyst (section 3.6.), which might have enhanced properties. For example, *peri*-substituents were found to increase the configurational stability of [5]helicenes.[131] While the reported synthesis involved a resolution, the tetrafluoro

binaphthalene **14e** represents a promising intermediate for a stereoselective preparation of such a substituted [5]helicene **43** (Scheme 54).



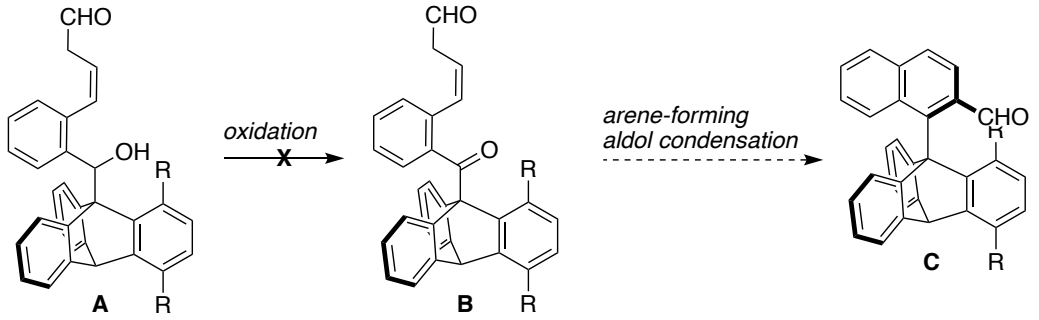
Scheme 54: The tetrafluoro binaphthalene **14e** as a potential precursor for the preparation of a disubstituted [5]helicene **43**.

3.7. Summary

Cyclization studies of poly-carbonyl compounds revealed the ability of small-molecule catalysts to trigger a noncanonical polyketide cyclization related to the conversion of poly-β-carbonyl compounds by the polyketide synthase machineries. The substrate synthesis involved the preparation of cinnamyl biindene precursors which were accessed through an oxidative dimerization or a Suzuki cross-coupling strategy. A remarkably efficient four-fold ozonolysis was developed to convert cinnamyl biindenes into the desired noncanonical hexa-carbonyl substrates containing a 1,2-diketone function. This allowed the synthesis of atropisomeric binaphthalene dicarbaldehydes distinct from oxidative dimerization processes and natural polyketides. Secondary amine catalysts bearing a hydrogen-bond donating side chain were identified to deliver the binaphthalene dicarbaldehyde products in high yields and good atroposelectivites, culminating in the first stereoselective preparation of the sterically demanding di-*peri*-substituted binaphthalene compound. Based on the mechanistic investigations of the arene-forming aldol condensation together with the observation of a symmetric reaction intermediate in NMR experiments, a double aldol addition followed by a double dehydration was hypothesized as a possible mechanism for the developed methodology. The significance of the developed double arene-forming aldol condensation was demonstrated through the straight-forward synthesis of a chiral diene ligand, an enantioenriched [5]helicene and the Maruoka ion-pairing catalyst from the binaphthalene dicarbaldehyde **14a**.

4. Stereoselective Synthesis of Csp^2-Csp^3 Atropisomers

Our group has a longstanding interest in addressing the challenges in the development of an atroposelective reaction for the synthesis of Csp^2-Csp^3 atropisomers and a first project was initiated by C. Fischer in the course of his Master thesis in 2014. He thereby targeted the preparation of a triptycene keto-aldehyde substrate. The triptycene unit was considered as an ideal scaffold for the sp^3-hybridized carbon providing three well-defined compartments. The keto aldehyde moiety was intended to utilize the arene-forming aldol condensation methodology for the stereoselective preparation of Csp^2-Csp^3 atropisomers. However, the triptycene scaffold was found to be a too sterically demanding Csp^3 unit, which was most probable inhibiting the final oxidation of a hydroxy function **A** to the required ketone **B** in order to explore the arene-forming aldol condensation to the Csp^2-Csp^3 atropisomer **C** (Scheme 55).[132]



Scheme 55: Studies of the stereoselective preparation of Csp^2-Csp^3-atropisomers with the arene-forming aldol condensation methodology investigated by C. Fischer.

Based on these insights, revealing difficulties to work with compounds bearing a triptycene unit, we envisioned to explore this unknown territory of stereoselective catalysis again, this time with a different approach including two major changes:

1. The triptycene molecule is a convenient scaffold concerning Csp^2-Csp^3 atropisomers if one of its three benzene units is substituted, providing three different, well-defined cavities in the final

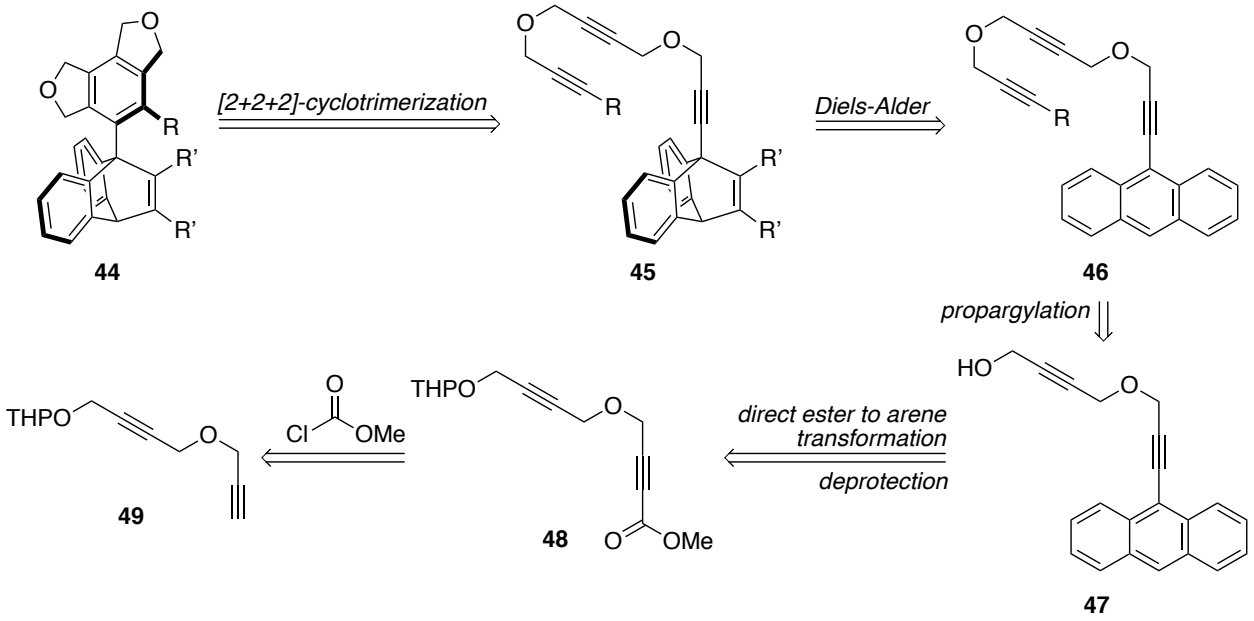
Csp^2-Csp^3 atropoisomeric product. Substituted triptycenes can be synthesized through Diels-Alder reactions with benzynes.[84] However, as challenges were noticed by C. Fischer attributed with the triptycene based molecules, we intended to examine a different sp^3-hybridized carbon framework. Replacement of one benzene unit of the triptycene with an ethylene group results in an ethenoanthracene structure which also belongs to the barrelene type molecules. Counterintuitively, ethenoanthracenes were found to provide an unexpectedly high rotational barrier for Csp^3-Csp^3 atropisomers allowing the separation of the (–*sc*)- and (+*sc*)-enantiomers through crystallization with (–)-menthol (section 1.5.5).[87] Ethenoanthracenes are conveniently synthesized through Diels-Alder reactions of anthracenes and alkynes, which is a more functional group tolerant strategy than the reactions with benzyne. Furthermore, the ethenoanthracene formation with anthracene directly delivers a tetrahedral carbon scaffold with two equivalent and one different substituent, which is needed in the substrate for a stereoselective synthesis of Csp^2-Csp^3 atropisomers. Considering these advantages compared to the triptycene, we intended to attach an ethenoanthracene unit to our substrate.

2. Besides the excellent applicability of the arene-forming aldol condensation for the stereoselective preparation of various configurationally stable Csp^2-Csp^2 axis in high atroposelectivity, the reaction generally suffers from long reaction times. This is critical due to possible isomerization over the course of the reaction when the obtained products have a low configurational stability. Furthermore, the reaction was found being sensitive to pronounced steric demand. Therefore, we envisioned to explore a [2+2+2]-cyclotrimerization to stereoselectively prepare Csp^2-Csp^3 atropisomers, since alkyne cyclotrimerization is a well-established method to prepare highly substituted arenes and aromatic heterocycles.[133] Since the groundbreaking work of Mori and co-workers in 1994 with the development of the first stereoselective methodology based on the *de novo* construction of an arene,[134] the [2+2+2]-cyclotrimerization evolved to one of the most utilized arene-forming reaction in stereoselective catalysis. A wide range of transition metals are applicable and particularly nickel, cobalt, iridium and rhodium have been used in [2+2+2]-cyclotrimerization reactions for the stereoselective construction of rotationally restricted axes including biaryls with heterocycles, configurationally stable atropisomeric aromatic amides and curved polyaromatics. The most active catalysts are generally based on rhodium providing high turnover numbers and short reaction times at ambient temperatures.[66,135] The [2+2+2]-cyclotrimerization was therefore anticipated as a suitable methodology for our aim.

4.1. Substrate Design

The substrate for a [2+2+2]-cyclotrimerization requires three alkynes for the formation of a benzene ring. The alkynes were planned being tethered for an intramolecular cyclotrimerization to prevent mixtures of products and to entropically favor the reaction. Linking the alkynes together through ether bridges seemed most promising since these etherification reactions are generally high yielding and numerous propargyl alcohols and halides are commercially available. For an atroposelective rather than diastereoselective reaction, the substrate must not possess any stereogenic element, but the three different cavities have to result from the Csp^3-unit. This requirement is fulfilled when the sp^3-hybridized carbon contains two equal substituents while the third one is different.

From a retrosynthetic point of view, the intended Csp^2-Csp^3 atropisomer **44** would be obtained from an intramolecular [2+2+2]-cyclotrimerization of the trialkyne **45**. The sp^3-hybridized carbon of **45** would be obtained through Diels-Alder reaction with the anthracene **46**. A third alkyne with the terminal residue of choice would by introduced by an etherification with the corresponding propargyl halide. The coupling of the dialkyne chain with the anthracene moiety was planned through a direct ester to arene transformation developed in our group.[136] The required methyl ester **48** could be derived from the literature known dialkyne **49** (Scheme 56).

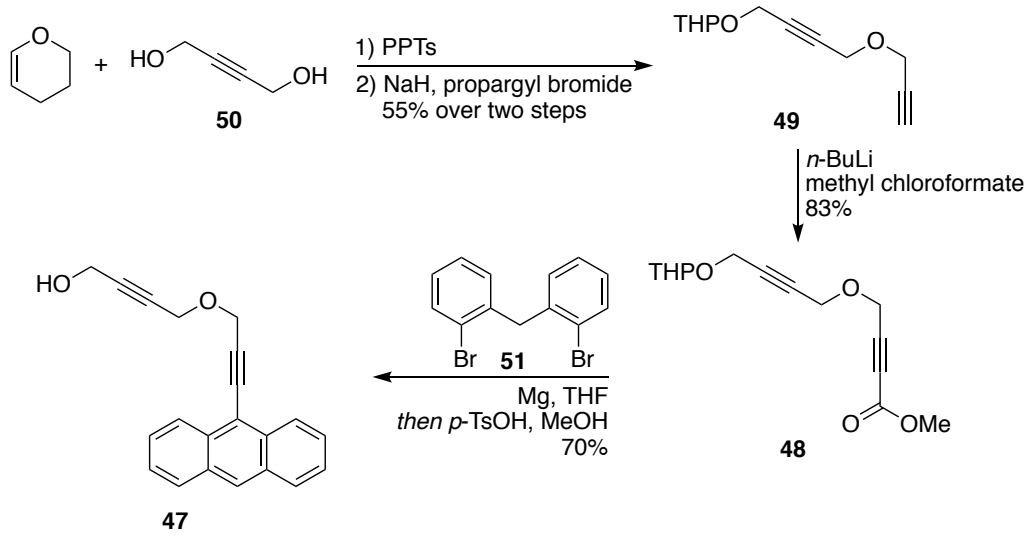


Scheme 56: Retrosynthetic analysis of the Csp^2-Csp^3-atropisomer **44**.

To verify the synthetic strategy, especially the applicability of the direct ester to arene transformation, which was so far not been explored with propiolic esters, **48** had to be synthesized first.

4.2. Substrate Synthesis

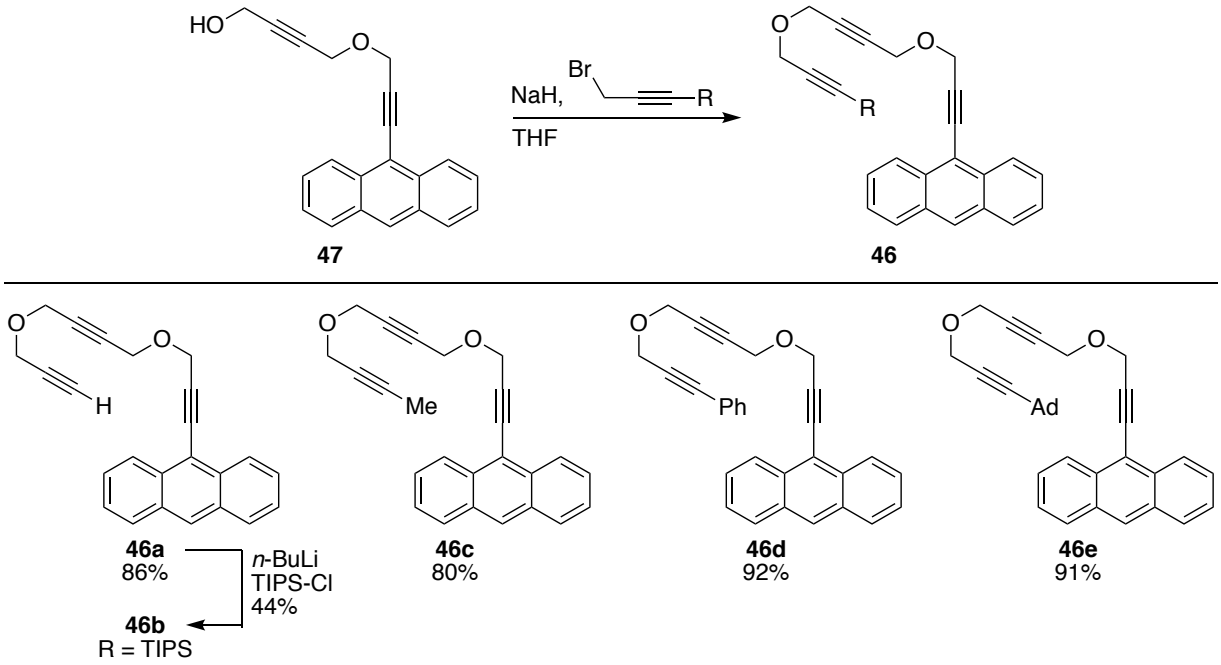
The dialkyne **49** was efficiently prepared through a desymmetrization of but-2-yne-1,4-diol (**50**) by a mono-protection with dihydropyran followed by an etherification of the second hydroxy function with sodium hydride and propargyl bromide in a yield of 55% over two steps. Deprotonation of the terminal alkyne of **49** with *n*-BuLi and addition of methyl chloroformate yielded the methyl ester **48** in 83%. To our delight, the propiolic ester **48**, a so far unexplored substrate for the direct ester to arene transformation, was efficiently converted with dibromide **51**[g] into the anthracene. The subsequent THP-deprotection with *p*-TsOH in methanol yielded the anthracene **47** in a good yield of 70% over two steps (Scheme 57).



Scheme 57: Synthesis of the dialkyne **47** through the direct ester to arene transformation.

With the dialkyne **47** in hand, a variety of trialkynes **46** were prepared through etherification with different propargyl bromides. The propargylation was generally applicable and high yields between 80% and 92% were obtained. The terminal unsubstituted trialkyne **46a** was further converted into a silylated trialkyne **46b** through deprotonation with *n*-BuLi and subsequent addition of TIPS-Cl in a moderate yield of 44% (Scheme 58).

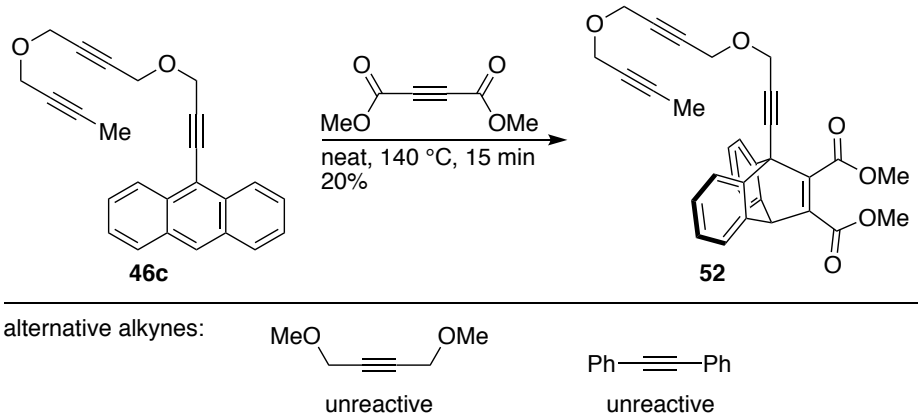
[g] Generously provided by Dr. Achim Link.



Scheme 58: Propargylation as a divergent strategy to access trialkynes **46a-e** from dialkyne **47**.

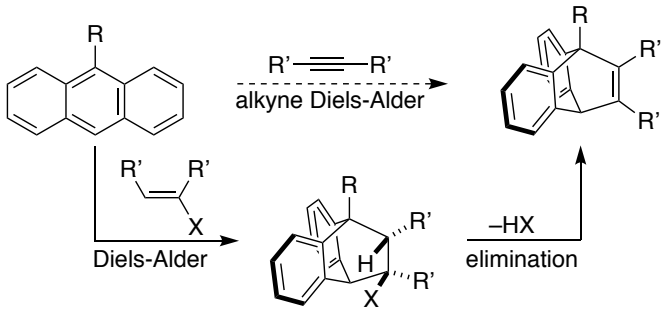
This third propargylation allowed to diverge the synthesis at a late stage, facilitating the preparation of various substrates with different terminal substituents. In solution, the anthracenes **46** generally decomposed within days and therefore had to be converted to more stable ethenoanthracenes rapidly.

The Diels-Alder reaction was first investigated with the methyl substituted trialkyne **46c** and dimethyl acetylene dicarboxylate as dienophile which was also used by Ōki and co-workers to prepare the ethenoanthracene for their Csp^3-Csp^3 atropisomers.[87] The reaction proceeded best under neat conditions at 140 °C albeit only a low yield of 20% for **52** was achieved, which could neither be improved by the use of solvents nor by lowering the temperature. Consequently, other symmetric alkynes as dienophiles were considered, which turned out being difficult. Readily available alkynes such as dimethoxy butyne or diphenyl ethylene were not reactive enough, while more reactive alkynes, for example acetylene dicarbaldehyde or dicyano acetylene are explosive and were therefore not considered (Scheme 59).[137–138]



Scheme 59: Diels-Alder reaction with anthracene **46c** and dimethyl acetylene dicarboxylate. On the bottom are alternative alkynes which were unreactive and no conversion of **46c** was observed.

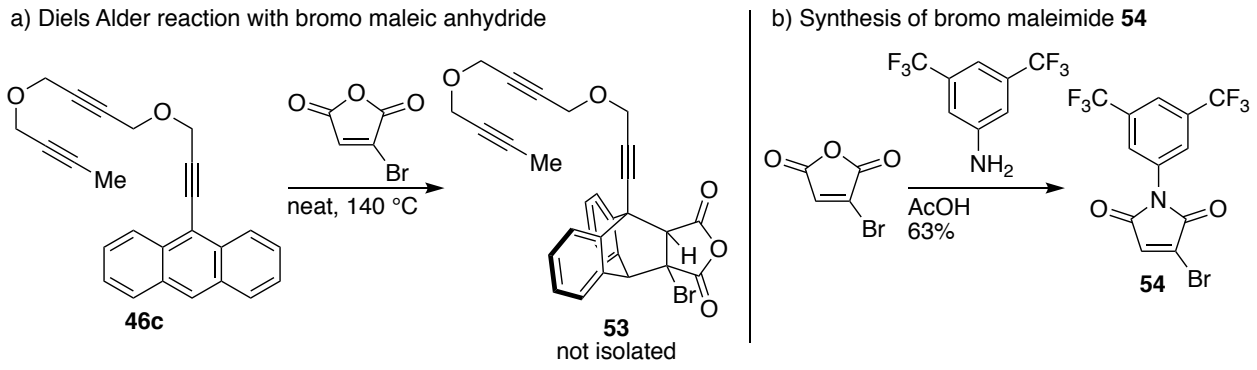
A two-step procedure involving a Diels-Alder reaction with an olefin followed by the elimination of an attached leaving group would be an alternative strategy to the alkyne Diels-Alder reaction. This strategy may allow to overcome the limited access of suitable alkynes and possibly even expand the substrate scope due to the large number of applicable olefins for Diels-Alder reactions (Scheme 60).



Scheme 60: Diels-Alder with an olefin as dienophile and subsequent elimination reaction as alternative strategy to the alkyne Diels-Alder reaction.

Supporting our notion, we could profit from a protocol by the the group of Snyder describing Diels-Alder reactions of bromo maleic anhydrides which proceeded in high regio- and diastereoselectivity with chiral anthracenes under thermal or Lewis acid catalyzed conditions.[139] If the bromide of the obtained Diels-Alder product can be eliminated, the bromo maleic anhydride could serve as an ideal alternative to the alkyne dienophiles. Compared to the work of Snyder and co-workers, the regioselective outcome of the Diels-Alder reaction would be negligible in our system since both isomers result in the same ethenoanthracene after the elimination step.

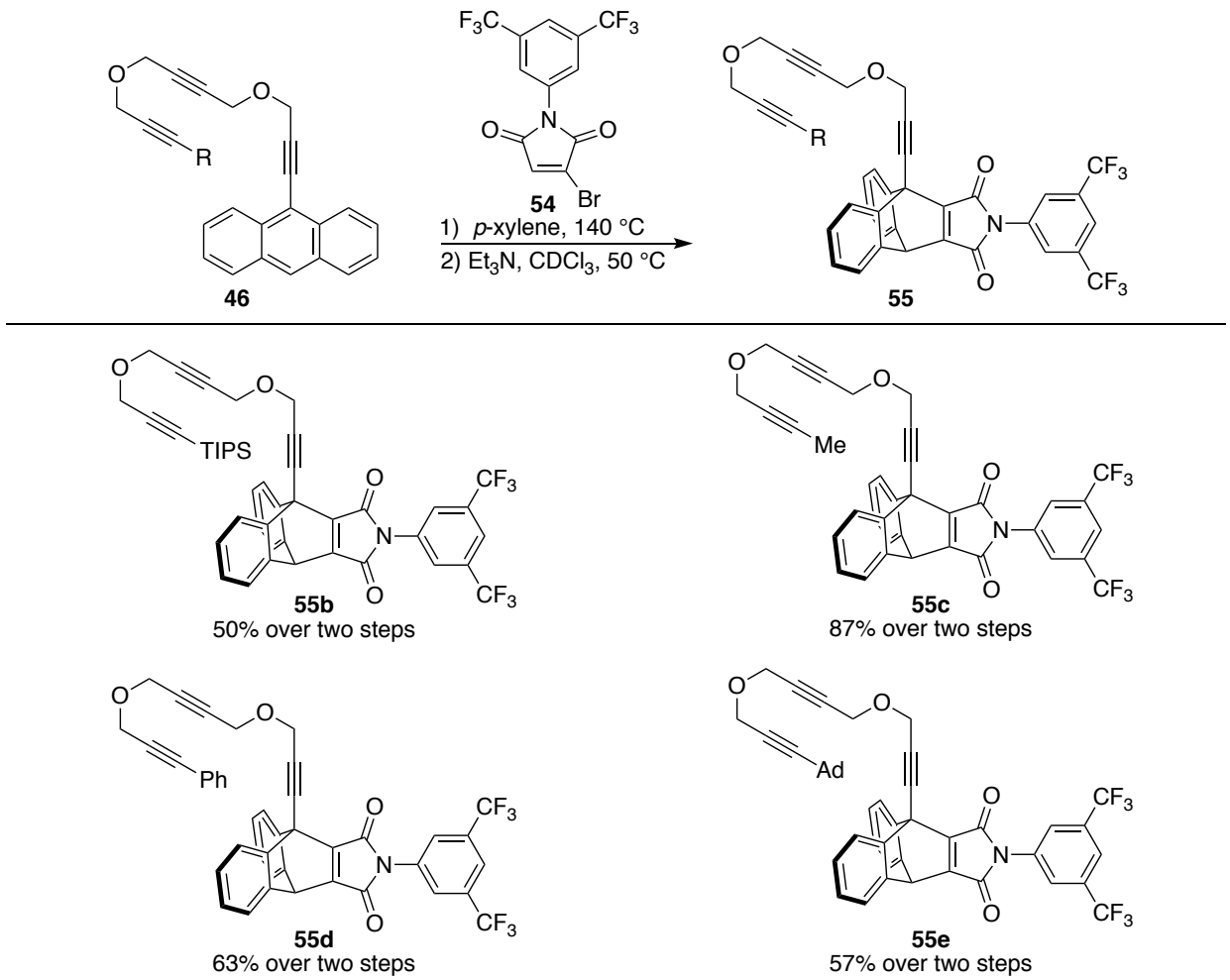
This concept was first examined with commercially available bromo maleic anhydride and anthracene **46c**. The Diels-Alder reaction was found to work best under neat conditions at 140 °C and full conversion of **46c** to one new product that was observed within only a few minutes. However, the product **53** could not be isolated by precipitation as described by Snyder and purification of the anhydride **53** by column chromatography was not possible (Scheme 61, a). Since the anhydride is very electrophilic, replacement of this functional group probably increases the stability of the Diels-Alder products. The conversion of the anhydride into a maleimide offers a straight forward access to a more stable functional group. Thus, the bis(trifluoromethyl)aniline was chosen as appropriate amine for this reaction to enhance the UV-activity of the ethenoanthracenes, which was found being unexpectedly low. This can be problematic in the determination of the enantiomeric ratio of the Csp^2-Csp^3 atropisomers by HPLC since the detection is based on UV-absorbance. Furthermore, the fluorine atoms might be advantageous to analyze the rotational isomers by ^{19}F NMR. The reaction of the bromo maleic anhydride with the 3,5-bis(trifluoromethyl)aniline proceeded smoothly in concentrated acetic acid and the maleimide **54** was obtained in a yield of 63% (Scheme 61, b).



Scheme 61: a) Diels-Alder reaction of anthracene **46c** and bromo maleic anhydride; b) Preparation of maleimide **54** from bromo maleic anhydride.

With the maleimide **54** in hand, the Diels-Alder reaction was examined with the anthracene **46c** and full conversion was observed in *p*-xylene at 140 °C after 30 minutes. Without purification, the bromide was eliminated under basic conditions with triethylamine in chloroform at 50 °C yielding the ethenoanthracene **55c** in an excellent yield of 87% over two steps. These reaction conditions were generally applicable and the anthracenes **46b-e** were converted into the final ethenoanthracene substrates **55b-e** in good yields of 50-87% yield over two-steps. Unfortunately,

the ethenoanthracene **55a** could not be isolated in pure form due to purification difficulties (Scheme 62).



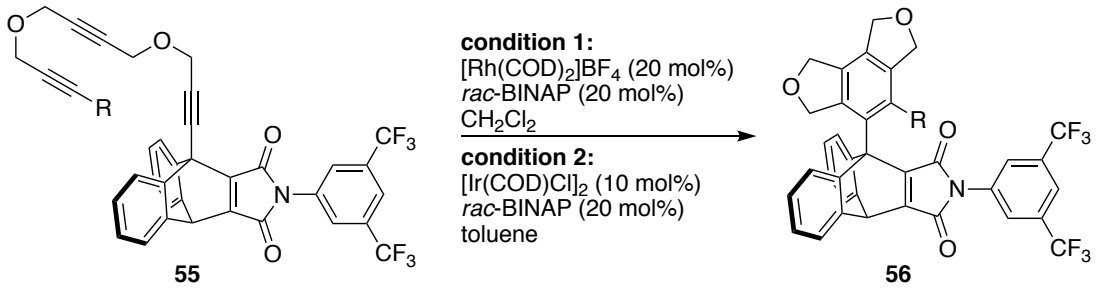
Scheme 62: Diels-Alder reaction with maleimide **54** and anthracenes **46b-e** followed by an elimination yielding the ethenoanthracenes **55b-e**.

4.3. The [2+2+2]-Cyclotrimerization

With the four ethenoanthracene substrates **55b-e** in hand, the [2+2+2]-cyclotrimerization was investigated. Thereby, the examination was focused on iridium and rhodium catalysts as they are most frequently used. Furthermore, these two metals generally do not require tailor-made ligands as for example with cobalt[140] and the highest selectivities are usually obtained with commercially available di-phosphine ligands.[66] The examination was commenced with the only silicon containing substrate **55b**, but no conversion was observed with $[Rh(COD)_2]BF_4$ as metal source and *rac*-BINAP as ligand in dichloromethane at 40 °C (Table 6, Entry 1). The TIPS-substituted

substrate **55b** is probably too sterically demanding and the investigations were continued with the substrate **55c** containing the smallest terminal substituent with a methyl group. Low conversion of **55c** (<10%) was obtained with a catalytic system of $[Ir(COD)Cl]_2$ and *rac*-BINAP in toluene at 70 °C (Table 6, Entry 2). The rhodium catalyst was found to be significantly more reactive and full conversion of the substrate **55c** was observed after 2 hours at room temperature. Only one product was observed by TLC and TLC-MS analysis supported the formation of the desired product **56c**. The rotation of the restricted axis was estimated to be in the range of the NMR time scale since broadening of the signals was observed. A low barrier to rotation was further confirmed by HPLC analysis on a chiral stationary phase where the product **56c** was detected as one sharp peak (Table 6, Entry 3). Comparable results were obtained for the phenyl-substituted substrate **55d** and again, broadening of the NMR signals was observed (Table 6, Entry 4). Hence, we were interested in analyzing the reaction with the substrate **55e**, where the steric demand is further increased by the adamantyl-substituent.[141] The reaction was much slower even with the more reactive rhodium catalyst and low conversion of starting material **55e** was observed after 36 hours at room temperature. The temperature was therefore increased to 40 °C for 24 hours but only 34% conversion was achieved. Nevertheless, we were pleased to detect three new compounds besides the starting material **55e** by TLC and for all three new spots on the TLC, the mass of the product **56e** was found by the TLC-MS, as a first indication of the formation of different diastereoisomers. NMR analysis of the crude reaction mixture displayed an approximate ratio of 1 : 1.2 : 2.2 for the three compounds. The major isomer could be isolated in pure form by preparative TLC. The other two compounds were always obtained as a mixture of two or all three diastereoisomers even with immediate NMR analysis after the isolation and careful evaporation of the solvent at low temperatures. The rapid interconversion of these diastereoisomers is indicative for a low rotational barrier. This postulation was further supported by HPLC analysis on a chiral stationary phase. The enantiomers of the major diastereoisomer could be separated well, while more than two peaks were observed for the other two diastereoisomers. A repeated measurement of all three samples after three days at room temperature resulted in a similar chromatogram for all three compounds. (Table 6, Entry 5).

Table 6: Examination of the [2+2+2]-cyclotrimerization of the prepared substrates **55b-e**.



Entry	Substrate	Conditions	Time [h]	Observation
1	**55b**	1	48[a]	No conversion
2	**55c**	2	16[b]	<10% conversion, probably dimers
3	**55c**	1	2[c]	Full conversion, one new compound
4	**55d**	1	16[c] *then* 24[a]	Full conversion, one new compound
5	**55e**	1	36[c] *then* 24[a]	34% conversion, **three new compounds**

[a] Performed at 40 °C; [b] Performed at 70 °C, [c] Performed at room temperature

From the examination of the [2+2+2]-cyclotrimerization reaction with the ethenoanthracene substrates **55b-e**, we found promising evidence, that all three diastereoisomers of **56e** are formed from the adamantyl-substituted substrate **55e**. The barrier to rotation is high enough to separate the isomers by preparative TLC. However, interconversion of the isomers occurs within several hours. In order to develop an atroposelective methodology, the barrier to rotation is too low for achieving selectivity due to fast isomerization of the formed atropisomers during the reaction. Nevertheless, determination of the configuration eventually allows to correlate the important interactions inhibiting the interconversion with the configurational stability of the atropisomers. This will support the design of a next generation of substrates leading to Csp^2-Csp^3 atropisomers with higher barrier to rotation.

4.4. Rotational Profile of the Csp^2-Csp^3 Atropisomers

The conformational analysis was initiated with a detailed investigation of the major diastereoisomer as it is the most stable one and can be isolated in pure form. Since the rotation takes place in the range of hours, HPLC analysis was considered a convenient method to investigate the interconversion. The enantiomers of the major diastereoisomer were separated by HPLC and then reinjected over time to follow the interconversion over time. Simultaneous to the decrease of the pure enantiomer, an increase of the other diastereoisomers was observed before the other

enantiomer of the major diastereoisomer appeared. A direct interconversion of the enantiomers of the major diastereomers was therefore not occurring. With the assumption that a full rotation around the restricted axis is possible, we hypothesized that the major diastereoisomer is the *synclinal* conformer, because this is the only isomer which cannot directly interconvert into its enantiomer without the formation of the other diastereoisomers (Figure 17).

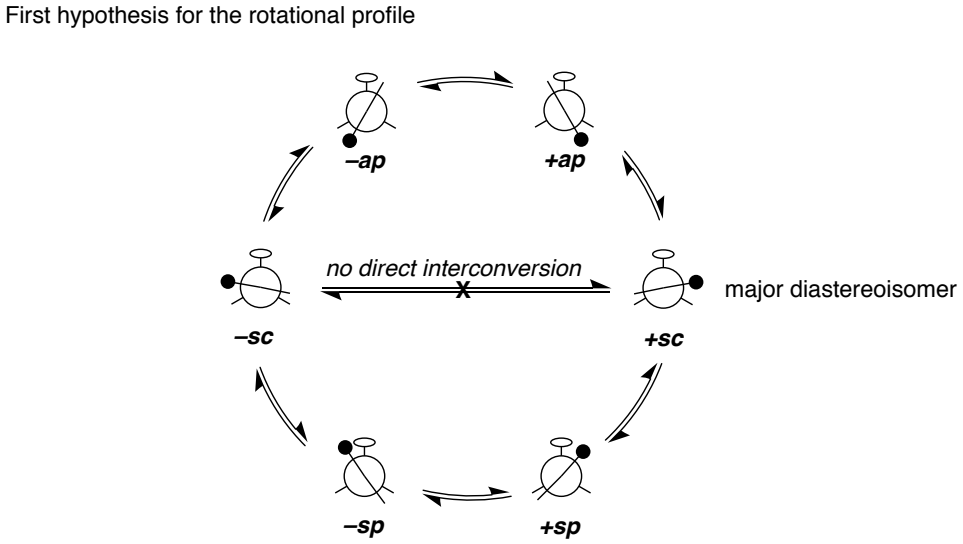


Figure 17: First hypothesis for the different Csp^2-Csp^3 atropisomers of compound **56e** where the major diastereoisomer is assumed being the *(±sc)*-conformer which cannot racemize through direct interconversion.

This conclusion would be in agreement with the results obtained from the HPLC analysis, however an observation in the TLC evaluation was contradicting this hypothesis. The three diastereoisomers appear pure in a TLC which was immediately made after the isolation. One hour later, the major diastereoisomer is still one spot (Figure 18, TLC spot a), while the other two diastereoisomers (Figure 18, spot b + c) appeared as a mixture, which indicated that they interconvert without the formation of the major diastereoisomer. Therefore, it is not possible that the major diastereoisomer has the *synclinal* conformation, since the *synclinal* conformer is necessarily formed in the interconversion of the *antiperiplanar* into the *synperiplanar* conformation (Figure 18).

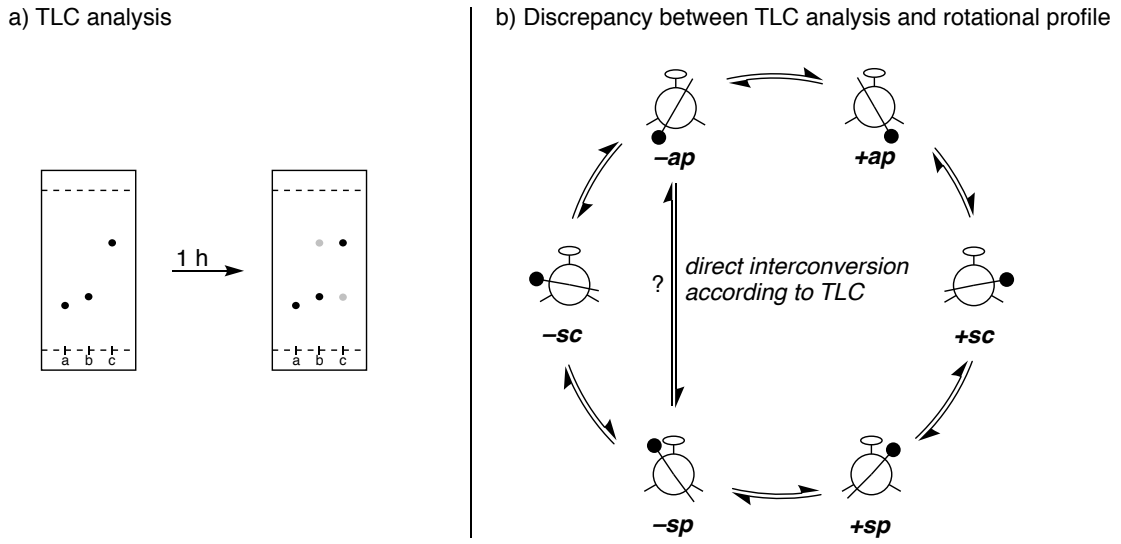


Figure 18: a) TLC analysis revealed a rapid interconversion of the two minor diastereoisomers (TLC spots b + c). b) The hypothesized rotational profile is contradicting to the TLC analysis since their interconversion has to go through the major diastereoisomer *(*±*sc*).

With the network of isomer interconversion displayed in Figure 17 and Figure 18, it is not possible to assign a conformation for the major diastereoisomer, which is in agreement with both observations from the HPLC and TLC analysis. Consequently, it is questionable whether this model is correct.

Until now, a full rotation around the restricted axis was assumed as possible. However, a high barrier which for example prohibits the interconversion of the (*–ap*)- into (*+ap*)-isomers would also be in agreement with the data of the HPLC studies. The pure (*–ap*)-isomer has to pass through all conformers in order to interconvert into the (*+ap*)-isomer. Furthermore, the observation of the TLC analysis is also supporting this working model because the interconversion of the other two diastereoisomers (*sc* and *sp*) can take place without passing through the (*ap*)-isomer. Based on the fact that the minor isomers interconvert first, it can be concluded that the second highest rotational barrier is between the (*ap*)- and the (*sc*)-isomers. Further support for this model was obtained from the characterization of the major diastereoisomer by NMR. NOE correlations between the adamantyl group and the bis(trifluoromethyl)benzene as well as between the dihydrofuran moiety with both benzene units of the ethenoanthracene confirmed the (*ap*)-conformation of the major diastereoisomer, which maintained the hypothesis of a high rotational barrier between the enantiomers of the (*ap*)-isomer (Figure 19).

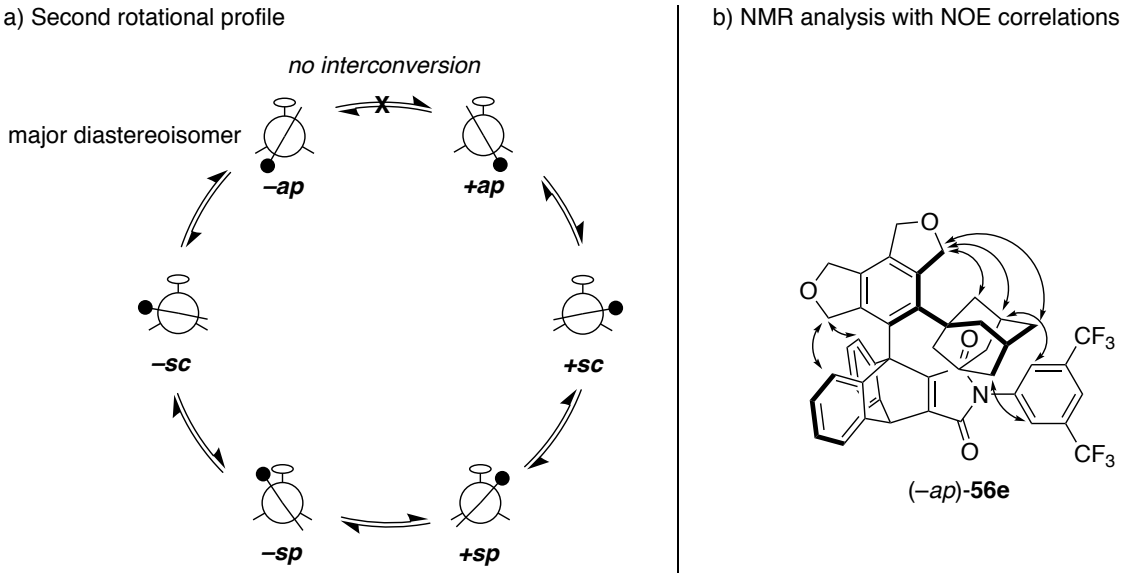


Figure 19: a) The major diastereoisomer of the [2+2+2]-cyclotrimerization of the adamantyl substrate **55e** was identified as the (*ap*)-**56e**; b) The arrows indicate the measured NOE which allowed to determine the relative the isomer conformation by NMR.

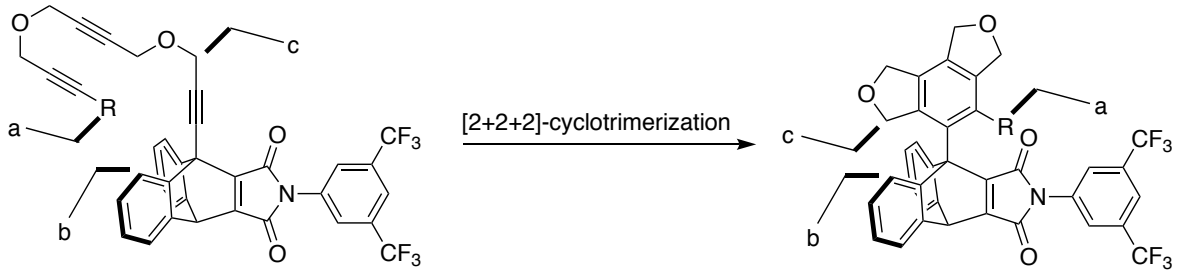
With the determination of the rotational profile and the assignment of the major product being (*ap*)-**56e**, the relative interconversion barriers could now be attributed to the molecular structure enabling to estimate the impact of the functional groups to the configurational stability. The carbonyl function of the imide represents a substantial barrier for the adamantyl group while rotation over the benzene units of the ethenoanthracene occurs fast. Compared to the adamantyl moiety, the dihydrofuran can rotate fast over the carbonyl of the imide as observed in the interconversion of the enantiomers of the (*ap*)-isomer. Thus, the dihydrofuran has a significantly lower impact on the barrier to rotation compared to adamantyl group as the second *ortho*-substituent of the newly formed benzene ring. Conclusively, the variation of the dihydrofuran moiety appeared more advantageous compared to the adamantyl unit to increase the configurational stability of the Csp^2-Csp^3 atropisomers.

Extensive analysis by TLC, HPLC and NMR revealed that the major diastereoisomer obtained in the [2+2+2]-cyclotrimerization of the ethenoanthracene **55e** is the (*ap*)-conformer. A high rotational barrier is observed between the (*–ap*)- and the (*+ap*)-conformer inhibiting a full rotation around the axis due to enhanced steric interactions between the adamantyl substituent and the carbonyl function of the imide. On the other hand, a low barrier to rotation was observed between the dihydrofuran and the imide by the interconversion of the enantiomers of the (*ap*)-conformer.

These valuable insights in the rotational profile confirmed that the obtained Csp^2-Csp^3 atropisomer are not stable enough to develop a protocol to prepare them stereoselectively. Furthermore, the dihydrofuran was identified as a relevant part considering modifications of the substrate to achieve higher configurational stability of the atropisomers.

4.5. The Carbonyl Substrate

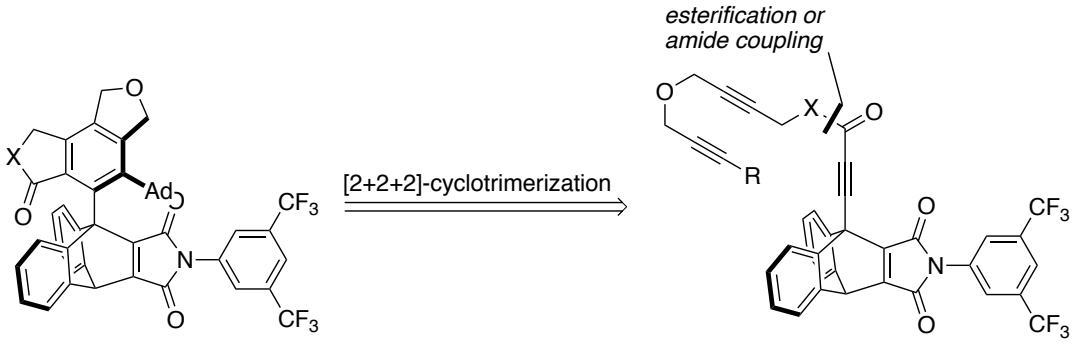
Evaluating the structure of the Csp^2-Csp^3-atropisomeric product obtained by the [2+2+2]-cyclotrimerization, three positions were considered as relevant for increasing the configurational stability of the products. The most straight-forward position to modify is the terminal position of the alkyne chain through variation of the propargyl bromide, is the etherification to introduce the third alkyene (section 4.2.). Considering the encouraging results obtained with the adamantyl substituent when compared to the other examined substituents in the former evaluation (section 4.3.), we decided to maintain the adamantyl unit as the terminal substituent and modify one of the other two indicated positions (Scheme 63, position a). While the adamantyl group is capable to rotate over the benzene units of the ethenoanthracene, a significantly higher barrier was observed for the imide. Thus, the introduction of substituents in the 1-position of the benzene moieties would lead to an increased steric repulsion towards the adamantyl group and therefore potentially increase the barrier to rotation. Nevertheless, the reaction with **55e** was already very slow and full conversion of the substrate was not achieved even with reaction times of 2.5 days. A further increase of the steric demand of the ethenoanthracene might lead to an even lower conversion of the substrate. Additionally, a further increase in steric demand could lead to a ground state destabilization and thus to rather a decreased than increased barrier to rotation (section 1.5.3). Consequently, we did not consider to modify the 1-position of the benzene units (Scheme 63, position b). The third considerable part to modify was the dihydrofuran unit, which is a significantly smaller *ortho*-substituent of the benzene ring compared to adamantyl group. Instead of ether bridges to tether the alkynes for cyclotrimerizations, the linkage through a malonate or N-tosyl units would be applicable. However, replacement of the ether function itself would probably have only a small influence on the rotational barrier. Modification of the carbon in *ortho*-position of the benzene unit appeared as more promising due to the proximity to the restricted axis. Ideally, the modification will have a large impact on the rotational barrier with a low steric demand to avoid deceleration of the reaction (Scheme 63, position c).



Scheme 63: Positions in the substrate and the product which are expected to have an influence on the configurational stability of the Csp^2-Csp^3 atropisomers.

4.5.1. Substrate Design

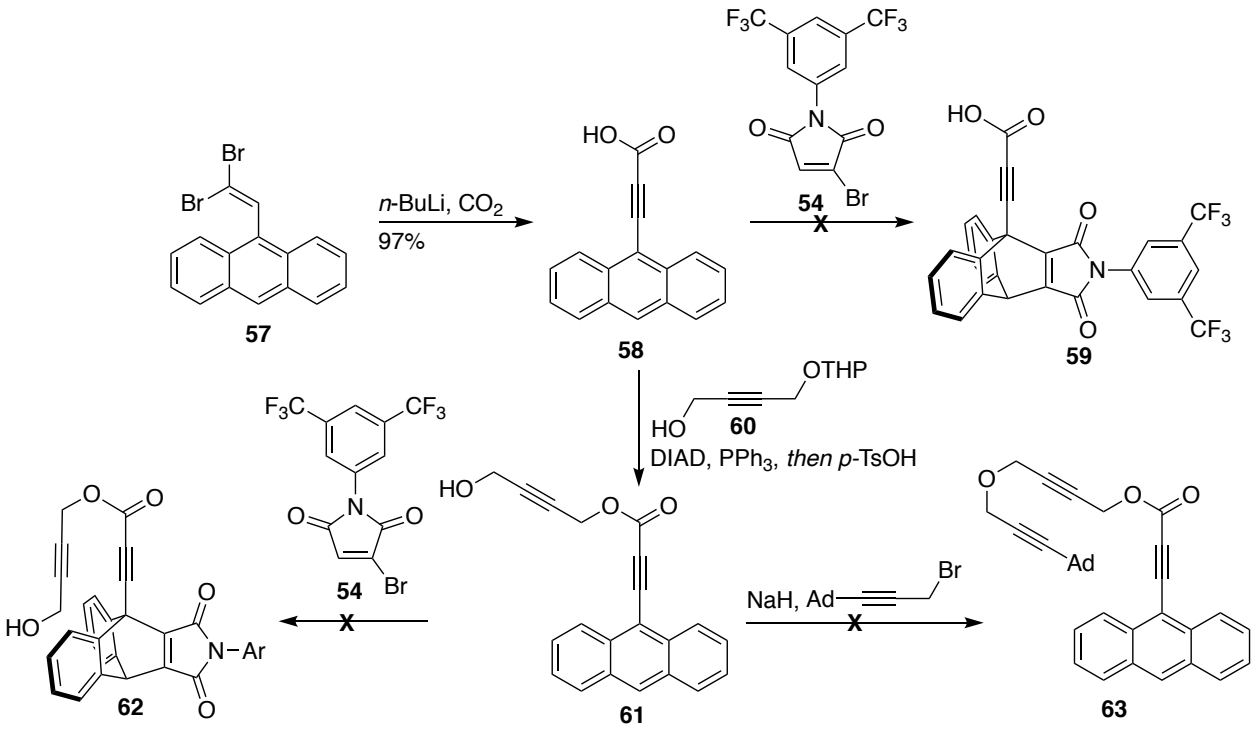
The investigations of the rotational profile of the atropisomers of (*ap*)-**56e** have shown that the carbonyl function of the imide provides a meaningfully high barrier which inhibits a full rotation around the Csp^2-Csp^3 axis. A second carbonyl function on the Csp^2 part of the restricted axis would therefore be a reasonable option as modification. Two carbonyl functions pointing into the cavities from opposite sites possibly lead to an interlocked system with a substantial rotational barrier enabling the development of a stereoselective methodology to prepare Csp^2-Csp^3 atropisomers. Furthermore, the hybridization of the carbon in *ortho*-position of the benzene ring would change from sp^3 in the dihydrofuran to sp^2 for the carbonyl function. This leads to a decreased steric demand in the *ortho*-position, potentially enhancing reactivity of the substrate. The carbonyl function could be introduced in the form of a ketone, an ester or an amide. Anhydrides were not considered due to potential stability issues as previously observed (section 4.2.). Esterification or amide coupling of an ethenoanthracene bearing a carboxylic acid with a dialkyne bearing a terminal hydroxy or amine function were regarded as a promising strategy to introduce the carbonyl function. (Scheme 64).



Scheme 64: Intended introduction of a carbonyl function as ester or amide to increase the configuration stability of the Csp^2-Csp^3-atropisomers.

4.6. Synthesis of the Carbonyl Substrate

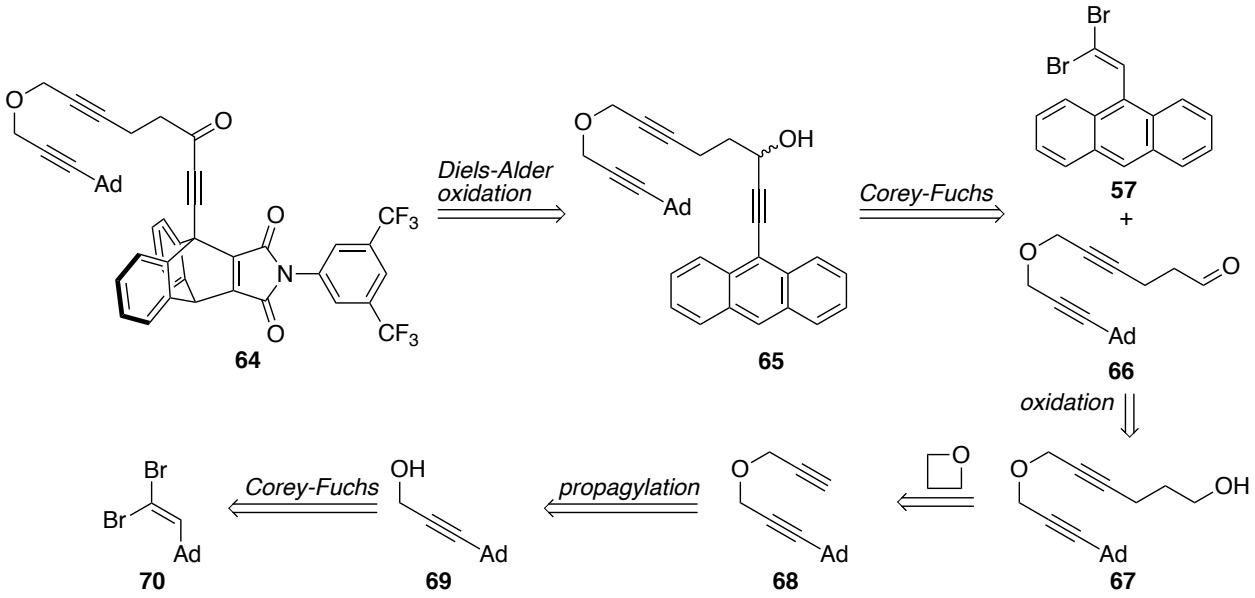
The introduction of the carbonyl function as an ester was examined first. Thus, the carboxylic acid **58** was prepared from divinylbromo anthracene **57** in a Corey-Fuchs reaction with subsequent treatment with carbon dioxide in an excellent yield of 97%. Further conversion of **58** into the ethenoanthracene by the Diels-Alder reaction with the maleimide **54** was investigated, intending to perform the esterification as late in the synthetic sequence as late as possible. However, no conversion of the carboxylic acid **58** was observed. Since examining the low solubility of **58** is problematic, the dialkyne **61** was prepared from **58** through a mild esterification using Mitsunobu conditions. The purification of this compound was found to be difficult and **61** could not be isolated in pure form. Nonetheless, the Diels-Alder reaction with the maleimide **54** was explored, but again no conversion of **61** was observed. The electron-withdrawing nature of the carboxylic acid and the ester is probably too deactivating that the anthracene is not reactive enough even if the mixture is heated to 140 °C. As a last attempt, the Diels-Alder reaction was planned to be examined again after the introduction of the third alkyne. However, the strongly basic conditions in the etherification completely cleaved the ester bond and the carboxylic acid **58** was recovered from the reaction mixture (Scheme 65).



Scheme 65: Attempts to prepare an ester containing trialkyne substrate from the carboxylic acid **58**.

Due to these issues in the synthesis of a trialkyne tethered through an ester function, we did not consider to investigate the amide substrate and turned our attention towards the preparation of a new substrate bearing a ketone.

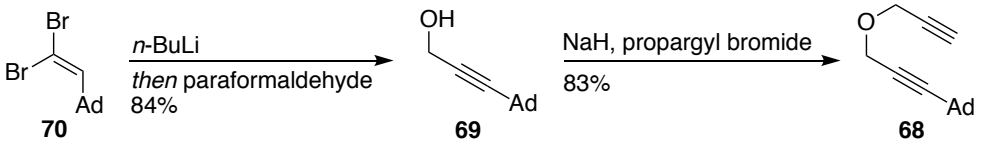
Having the problems from the synthesis of the ester substrate in mind, we aimed to develop a robust more than a step-economic synthesis of the substrate **64** containing a ketone in the alkyne chain. The substrate **64** could be accessed through oxidation of the hydroxy function of substrate **65** followed by a Diels-Alder reaction and elimination sequence. Alternatively, changing the order of reactions is possible if the ketone would have a negative influence on the reactivity in the Diels-Alder reaction. One alternative strategy to synthesize **65** is the addition of a lithiated dialkyne chain to an anthracene propiolaldehyde. However, no evidence for the existence of lithiated pent-4-yn-yl compounds was found in literature and was therefore not further considered. Formation of the other bond of the ketone appeared as more promising and could be realized through a Corey-Fuchs reaction of dibromovinyl anthracene **57** and dialkyne aldehyde **66**. If the oxidation of alcohol **67** to aldehyde **66** is feasible, we could profit from a literature-known procedure to prepare alcohol **67** from the terminal alkyne **68** and oxetane as a propanol-synthon.[142] The terminal alkyne **68** was planned to be synthesized by a propargylation of the literature known propargyl alcohol **69** (Scheme 66).[143]



Scheme 66: Retrosynthetic analysis of the trialkyne **64**.

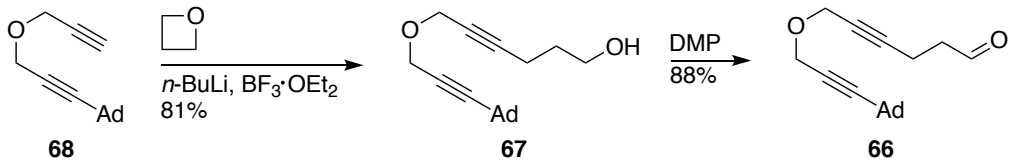
With this promising synthetic strategy to access the trialkyne substrate **64** in mind, we started the substrate synthesis with the preparation of the propargyl alcohol **69**. The preparation of

dibromovinyl adamantane **70** in a Ramirez reaction with adamantane carbaldehyde was described by the group of Zhu.[144] The dibromovinyl adamantane **70** could be used as starting material for the Corey-Fuchs reaction to the ethynyladamantane. Finally, the preparation of the propargyl alcohol **69** from ethynyladamantane via deprotonation of the terminal alkyne and addition of paraformaldehyde was described by the group of Breit.[143] Notably, the Corey-Fuchs reaction and the substitution of the terminal alkyne might be combined with trapping the acetylide in the Corey-Fuchs reaction with electrophiles as already mentioned in the original publication.[145] Indeed, paraformaldehyde was added to the reaction mixture after the reaction of the dibromovinyl adamantane **70** with *n*-BuLi and the propargyl alcohol **69** was isolated in a good yield of 84%. The propargylation with propargyl bromide was performed under identical conditions as used previously (section 4.2.) and the dialkyne **68** was obtained in a good yield of 83% (Scheme 67).



Scheme 67: One pot procedure to prepare propargyl alcohol **69** from dibromovinyl adamantane and propargylation of **69** to access the dialkyne **68**.

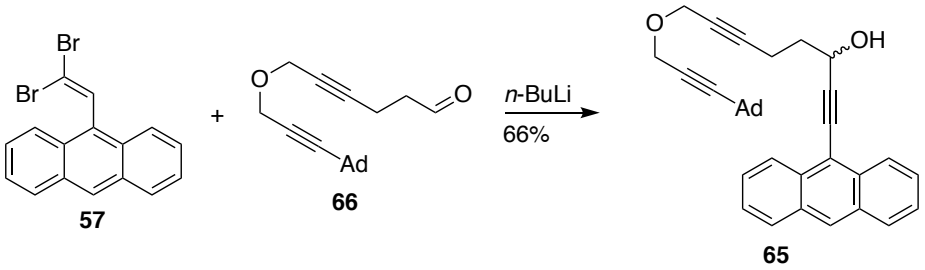
After the efficient preparation of the dialkyne **68**, the introduction of the propanol unit by the use of oxetane was examined following a protocol developed by Yamaguchi and co-workers.[142] They described the preparation of various pent-4-yn-ols through the ring opening of oxetanes by lithiated acetylides. For sufficient activity, the oxetane required activation by a Lewis acid. This protocol was also applicable in our synthesis and the alcohol **67** was obtained in a good yield of 81%. The oxidation of alcohol **67** using DMP proceeded smoothly and the aldehyde **66** was isolated in 88% yield (Scheme 68).



Scheme 68: Synthesis of the aldehyde **66** through introduction of the propanol unit via a Lewis acid catalyzed oxetane opening followed by a DMP oxidation of the alcohol **67.**

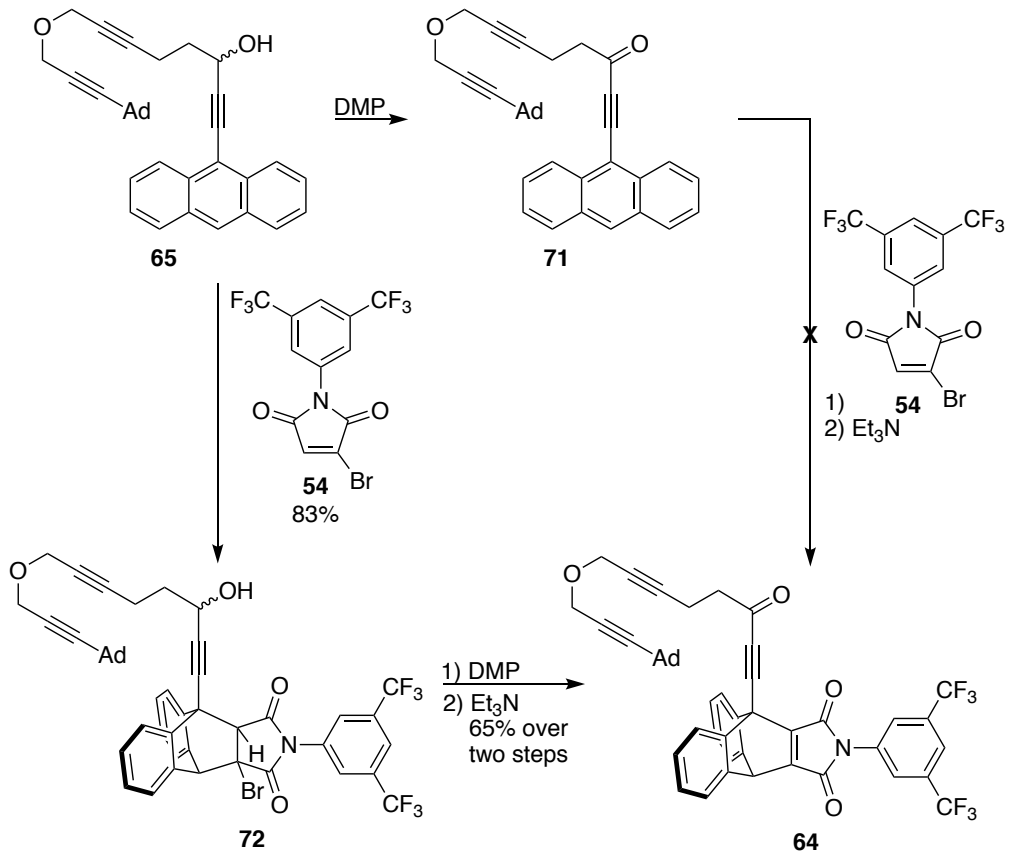
A further Corey-Fuchs reaction was performed to couple the dialkyne aldehyde **66** to the anthracene and simultaneously forming the third alkyne, which is needed for the intramolecular [2+2+2]-cyclotrimerization. Hence, the dibromovinyl anthracene **57** was converted into the lithium

acetylide using *n*-BuLi and the aldehyde **66** was directly added to the reaction mixture. This simultaneous alkyne formation and coupling of the two substrate parts proceeded efficiently and the alcohol **65** was isolated in 66% yield (Scheme 69).



Scheme 69: Corey-Fuchs reaction to couple the dialkyne chain to the anthracene moiety.

For the final transformations of the anthracene **65** into the ethenoanthracene **64**, we decided to oxidize the alcohol before the Diels-Alder-elimination sequence to prevent the possible dehydration of the hydroxy function under the basic conditions used for the elimination. In a test reaction, the alcohol **65** was readily oxidized to the corresponding ketone **71** with DMP but no conversion of the corresponding anthracene was observed in the Diels-Alder reaction. The keto functionality probably deactivates the anthracene moiety for the Diels-Alder reaction similarly to the carboxylic acid **58** and the ester **61** (Scheme 65). Therefore, the reaction sequence was explored in the reversed order and the Diels-Alder reaction with the alcohol **65** was found to be a selective and smooth reaction and full conversion of **65** was obtained in only 1.5 hours. Different to the previous Diels-Alder-elimination sequences (section 4.2.), it was crucial to purify the Diels-Alder product **72** prior to the elimination. Without purification, poor yields were obtained due to an undesired oxa-Michael addition of the Diels-Alder product to the excess maleimide **54**. With the adjusted reaction conditions, the alcohol **72** was obtained in 83% yield. Finally, the Diels-Alder product **72** was eliminated with triethylamine and then oxidized with DMP yielding the desired ethenoanthracene substrate **64** in 66% yield. (Scheme 70).



Scheme 70: The synthesis of the ketone substrate **64** proceeded smoothly if the Diels-Alder elimination sequence was performed before the oxidation.

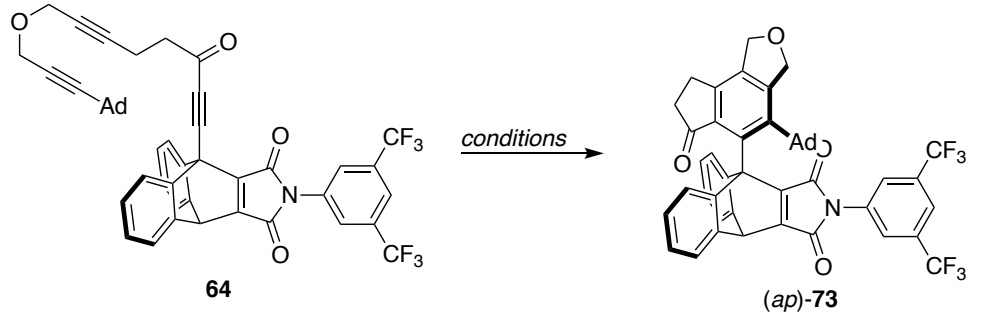
A novel substrate synthesis had to be developed in order to incorporate a keto functionality into the trialkyne chain. Nevertheless, the successful application of the Corey-Fuchs reaction enabled to accomplish the substrate synthesis of **64** in good to excellent yields for every step.

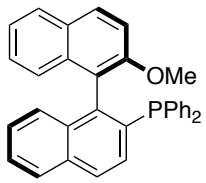
4.6.1. Configurationally Stable Csp^2-Csp^3 Atropisomers

To validate if the ketone is beneficial for the configurational stability of the Csp^2-Csp^3-atropisomer, the [2+2+2]-cyclotrimerization of the new substrate **64** was explored. A first evaluation was focused on different transition metal catalysts. Thereby, the four most common transition metals for [2+2+2]-cyclotrimerizations nickel, iridium, cobalt and rhodium were investigated. For nickel, the procedure of Mori and co-workers using (*R*)-MOP **lig1** as ligand was examined, but even at elevated temperatures, no conversion of the substrate **64** was observed (Table 7, Entry 1).[134] Changing to (*S*)-BINAP as a ligand in toluene at 100 °C did not lead to any conversion (Table 7, Entry 2). Iridium was combined with (*S*,*S*)-chiraphos **lig2** according to a literature procedure developed for the atroposelective synthesis of sterically demanding biaryls.[146] However, no

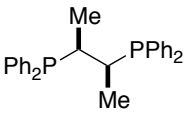
conversion was detected for this catalytic system (Table 7, Entry 3). Traces of conversion were obtained with (*S*)-SEGPHOS **lig3** in toluene at 100 °C (Table 7, Entries 4). The cobalt analogue of Wilkinson's catalyst $Co(PPh_3)_3Cl$ was described by the group of Hapke as a highly reactive catalyst for the [2+2+2]-cyclotrimerization of functionalized triynes, but also cobalt did not lead to conversion of **64** (Table 7, Entry 5).

Table 7: Examination of different transition metals for the intramolecular [2+2+2]-cyclotrimerization of **64** to the Csp^2-Csp^3-atropisomer **73**

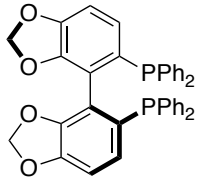




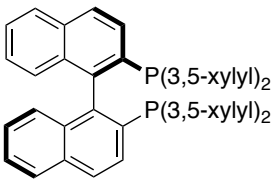
lig1



lig2



lig3



lig4

Entry[a]	Metal	Ligand	Solvent (Temperature)	Observation
1	$Ni(COD)_2$	**lig1**	THF (50 °C)	No conversion
2	$Ni(COD)_2$	(*S*)-BINAP	toluene (100 °)	No conversion
3	$[Ir(COD)Cl]_2$	**lig2**	xylene (50 °C)	No conversion
4[b]	$[Ir(COD)Cl]_2$	**lig3**	toluene (100 °C)	Traces of conversion
5[b]	$Co(PPh_3)_3Cl$	-	toluene (80 °C)	No conversion
6	$[Rh(COD)_2]BF_4$	**lig4**	DCE (50 °C)	50% conversion, traces of (*ap*)-**73**, e.r. = 78:22

[a] Performed with 15.0 μmol of **64** at a concentration of 3.00 $mmolL^{-1}$; [b] With $AgBF_4$ as additive.

Finally, around 50% conversion was observed with rhodium in combination with (*R*)-DM-BINAP **lig4**, confirming the applicability of this transition metal for the intended cyclotrimerization. The majority of the formed products were found to be a mixture of dimers resulting from an intermolecular [2+2+2]-cyclotrimerization. However, trace amounts of a desired conformer of **73** were isolated (Table 7, Entry 6). Detailed analysis by NMR including NOE experimentation

revealed that the obtained product is the *antiperiplanar* conformer (*ap*)-**73**. The Csp^2-Csp^3 atropisomer (*ap*)-**73** was configurationally stable at ambient temperatures and a promising enantiomeric ratio of 78:22 was measured by HPLC, as a first proof of concept of the feasibility of a catalyst-controlled stereoselective synthesis of Csp^2-Csp^3 atropisomer. Atropisomerization studies indicated a remarkably high configurational stability and no interconversion was observed even at 100 °C in toluene.

4.7. Di-π-methane rearrangement

To further confirm the preparation of the Csp^2-Csp^3 atropisomer (*ap*)-**73** and eventually determine the absolute configuration of the enriched enantiomer, an X-ray structure of (*ap*)-**73** was anticipated. A first indication for (*ap*)-**73** being a solid was found by concentration of the HPLC samples. Crystals suitable for X-ray analysis were obtained from slow evaporation of the solvent of an HPLC sample. To our surprise, the obtained structure contained a semi-bullvalene core instead of the expected Csp^2-Csp^3 axis (Figure 20).

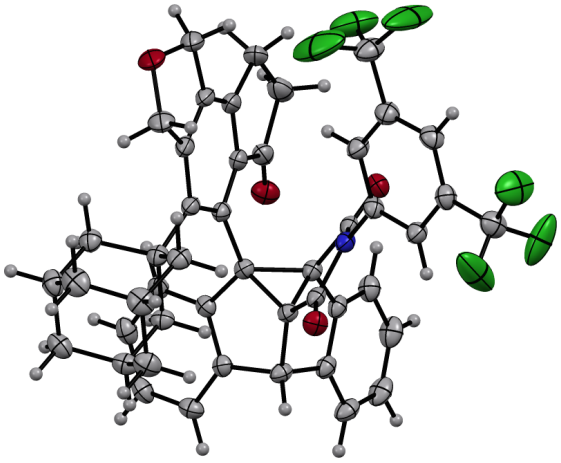
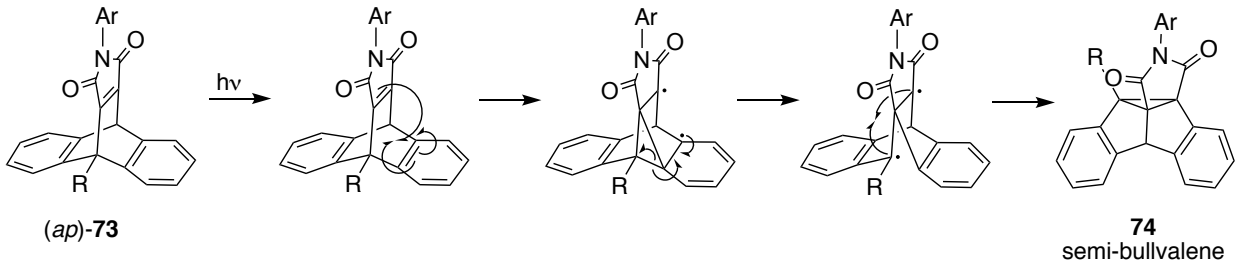


Figure 20: X-ray structure from an HPLC sample of (*ap*)-**73** revealing the formation of a semi bullvalene core.

This unexpected structure obviously raised the question how the (*ap*)-**73** was converted into the semi-bullvalene compound. Several literature reports described that ethenoanthracenes are prone to undergo a photochemical di-π-methane rearrangement to semi bullvalene structures, which was reported for the first time by Ciganek already in 1966.[147] Since then, the influence of substituents in the rearrangement was studied and the regioselectivity of the di-π-methane rearrangement was found being controllable depending of the nature of the substituent.[148–150] During the evaporation

of the solvent to obtain the crystals, the vial was standing on the bench and was therefore exposed to light. Hence, a light induced di-π-methane rearrangement of (*ap*)-**73** is feasible. To test whether the rearrangement occurred during the evaporation, the sample with the crystals from the X-ray analysis was resubjected into HPLC. The initially measured peaks were not observed anymore while two new peaks appeared. The complete absence of the initially obtained peaks clearly indicated that the di-π-methane rearrangement of (*ap*)-**73** occurred during the crystallization process. Moreover, the rearrangement was found to be stereospecific. Afterwards, we noticed that this rearrangement-product was observed in trace amounts in previous measurements. The mechanism is proposed to be initiated by a photoinduced cyclopropane diradical formation. Thereby, one radical is stabilized in the α-position of the amide and the second is delocalized through the aromatic ring. The bond between the bridgehead and the benzene radical is homolytically cleaved with the rearomatization as driving force. The radical is stabilized in the double benzylic position. Finally, the cyclopropane is formed through recombination of the radicals resulting in the semi bullvalene-structure (Scheme 71).



Scheme 71: Proposed mechanism for the di-π-methane rearrangement of (*ap*)-**73.**

4.8. Optimization of the [2+2+2]-Cyclotrimerization[h]

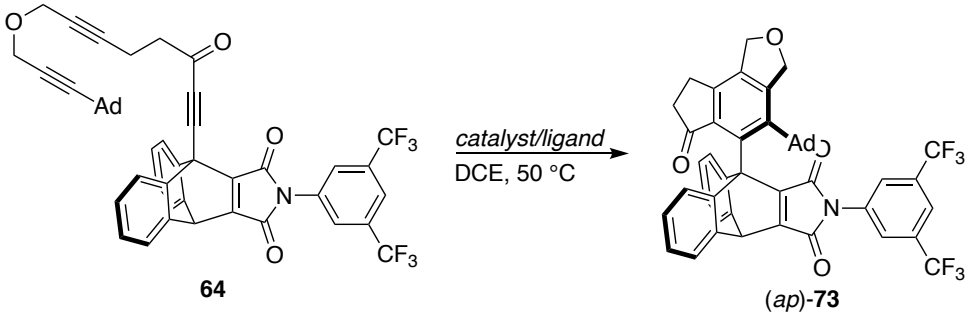
Having established a [2+2+2]-cyclotrimerization for the preparation of configurationally stable Csp^2-Csp^3 atropisomers, rhodium catalysts with different ligands were explored in order to reduce the undesired dimer formation, further increase the enantiomeric ratio of the (*ap*)-**73** and ideally finding a catalytic system leading to the formation of the two other conformers (*sc*)-**73** and (*sp*)-**73**.

[h] The optimization of the [2+2+2]-cyclotrimerization was performed together with Dr. Xingxing Wu.

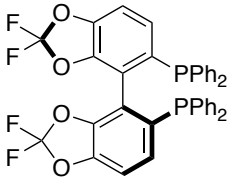
4.8.1. Examination of Ligands

The cationic $[Rh(COD)_2]BF_4$ was confirmed as an applicable metal source and the optimization was focused on the influence of different ligands. High catalytic activity was observed with (*S*)-H_8-BINAP as ligand leading to full conversion of the substrate **64** in only 2 hours. However, mainly the formation of dimers and even trimers was observed. Trace amounts of (*ap*)-**73** were isolated with an e.r. of 76:24 (Table 8, Entry 1). The dimer and trimer formation was completely suppressed with (*R*)-DTBM-SEGPHOS as ligand but the conversion remained at a maximum of 9% even with an extended reaction time. Additionally, the (*ap*)-**73** was formed racemically (Table 8, Entry 2). Similar results were obtained for the related (*S*)-SEGPHOS **lig3** and (*R*)-DM-SEGPHOS. The electro-deficient (*S*)-DIFLUORPHOS **lig5** resulted in full conversion of **64** but (*ap*)-**73** was isolated in only 10% yield and a moderate enantioselectivity of 58:42 (Table 8, Entry 3). Neither suppression of the dimer formation nor improvement of the enantioselectivity was observed with (*S*,*S*)-DIOP **lig6** as a ligand (Table 8, Entry 4). With the mono-dentate phosphine ligand *(S)*-Monophos **lig7**, the conversion of the substrate **64** was still only 10% but the reaction was highly chemoselective and the (*ap*)-**73** was the only compound detected besides the starting material **64**. Furthermore, the so far highest atroposelectivity of 20:80 was obtained (Table 8, Entry 5). Based on this exciting result, a number of phosphonamidite ligands were examined and the best results were attained with **lig8** and **lig9**. With both ligands, full conversion of the substrate **64** was observed and the (*ap*)-**73** was isolated in good yields of 60%. Compared to the good yields, the enantioselectivity was only moderate of 60:40 and 62:38 (Table 8, Entries 6+7). Although good yields for the (*ap*)-**73** were obtained by the use of phosphonamidites ligands, the results were still not satisfying and the different ligand structures were examined. Compared to the binaphthyl scaffold, the spiro-biindene backbone of **lig10** had only minor influence on chemoselectivity of the catalytic system. A good conversion of 80% was observed but the (*ap*)-**73** was isolated in only 20% yield. However, a major improvement in the enantioselectivity to 92:8 was achieved (Table 8, Entry 8). The high atroposelectivity underlined the applicability of the spiro ligand **lig10** for the [2+2+2]-cyclotrimerization, albeit the low yield of 20% for the (*ap*)-**73** indicated that further optimization was needed.

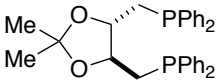
Table 8: Examination of ligands for the rhodium catalyzed [2+2+2]-cyclotrimerization.



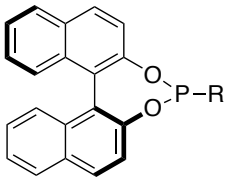
64 (*ap*)-**73**



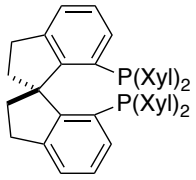
lig5



lig6



lig7 (R = NEt_2)
lig8 (R = NMe_2)
lig9 (R = NMeBn)



lig10

Entry[a]	Precatalyst	Ligand	Conversion	Yield (*ap*)-**73** / e.r.
1	$[Rh(COD)_2]BF_4$	(*S*)-H_8-BINAP	100%	Traces, e.r. = 24:76
2	$[Rh(COD)_2]BF_4$	(*R*)-DTBM-SEGPHOS	9%	8%, e.r. = 50:50
3	$[Rh(COD)_2]BF_4$	**lig5**	100%	10%, e.r. = 58:42
4	$[Rh(COD)_2]BF_4$	**lig6**	60%	15%, e.r. = 45:55
5	$[Rh(COD)_2]BF_4$	**lig7**	10%	10%, e.r. = 20:80
6	$[Rh(COD)_2]BF_4$	**lig8**	100%	60%, e.r. = 60:40
7	$[Rh(COD)_2]BF_4$	**lig9**	100%	60%, e.r. = 62:38
8	$[Rh(COD)_2]BF_4$	**lig10**	80%	20%, e.r. = 92:8

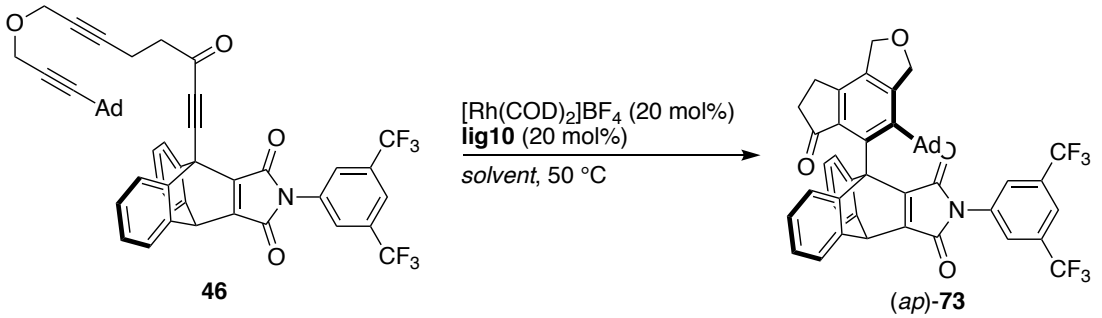
[a] Performed with 15.0 μmol of **64** at a concentration of 3.00 $mmolL^{-1}$ and with 20 mol% of catalyst precursor and 20 mol% of ligand.

A variety of different ligands have been examined for the cationic rhodium system. The active catalysts showed either poor chemoselectivity leading mostly to formation of dimers and trimers or (*ap*)-**73** was obtained in low atroposelectivity. On the other hand, for catalysts where the dimer and trimer formation was efficiently suppressed, the catalytic activity was either low or the (*ap*)-**73** was isolated in racemic from. However, the intriguingly high atroposelectivity of 92:8 indicated the applicability of the spiro ligand **lig10** for the stereoselective preparation of the Csp^2-Csp^3 atropisomers (*ap*)-**73**. Further optimization of the reaction conditions was thus necessary to additionally increase the yield of (*ap*)-**73**.

4.8.2. The Influence of Solvents

Additional optimization aiming to increase the yield and selectivity for (*ap*)-**73** were conducted with the exploration of different solvents under otherwise identical conditions with 20 mol% of rhodium catalyst and ligand **lig10** at a reaction temperature of 50 °C. No reaction occurred in tetrachloromethane (Table 9, Entry 1). Full conversion of the substrate **64** was observed in chlorobenzene, however in a modest ratio of 1:1 between the (*ap*)-**73** and dimers. The high level of enantioselectivity of 91:9 remained (Table 9, Entry 2). A favorable ratio of 1:0.35 for (*ap*)-**73** over the dimers resulted from reactions in *p*-xylene or toluene. For both solvents, a good enantiomeric ratio of 91:9 was obtained (Table 9, Entry 3+4). Fluorinated solvents were not beneficial for the cyclotrimerization and no product was formed in benzotrifluoride (Table 9, Entry 5). The highest chemo- and enantioselectivity was observed with *p*-xylene and toluene. Since both solvents generated equal results, toluene was chosen for further investigations of the counter-anion effect and to perform temperature studies.

Table 9: Exploration of the influence of the solvent.



Entry	Solvent	Ratio (*ap*)-**73** / dimers	e.r.
1	CCl_4	-	-
2	Chlorobenzene	1:1	91:9
3	*p*-xylene	1:0.35	91:9
4	toluene	1:0.35	91:9
5	benzotrifluoride	-	-

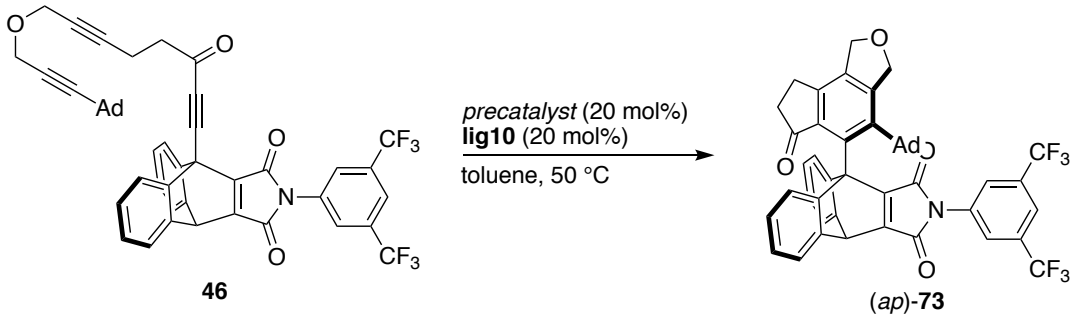
[a] Performed with 15.0 μmol of **64** at a concentration of 3.00 $mmolL^{-1}$.

4.8.3. The influence of the Counter-anion of the Precatalyst

Three different rhodium precatalysts were examined and compared to the $[Rh(COD)]_2BF_4$ (Table 10, Entry 1) to investigate the counter-anion effect. Tanaka and co-workers described reduced side-

product formation and higher enantioselectivities in a cationic rhodium catalyzed [2+2+2]-cyclotrimerization to prepare helicenes.[151] In our system, the triflate enhanced the chemoselectivity and no dimer formation was observed. However, the catalytic activity was much lower and the (*ap*)-**73** was obtained in 33% yield and a decreased enantioselectivity of 78:22 (Table 10, Entry 1). The hexafluoroantimonate and the weakly coordinating $B_{Ar}F$ anions completely inhibited the reaction and no conversion of **64** was observed for both (Table 10, Entries 3+4). Based on the considerable lower reactivity of all examined precatalysts, the evaluation of the optimal reaction temperature was conducted with the $[Rh(COD)]_2BF_4$ as rhodium source.

Table 10: Examination of the counter-anion effect of the precatalyst.



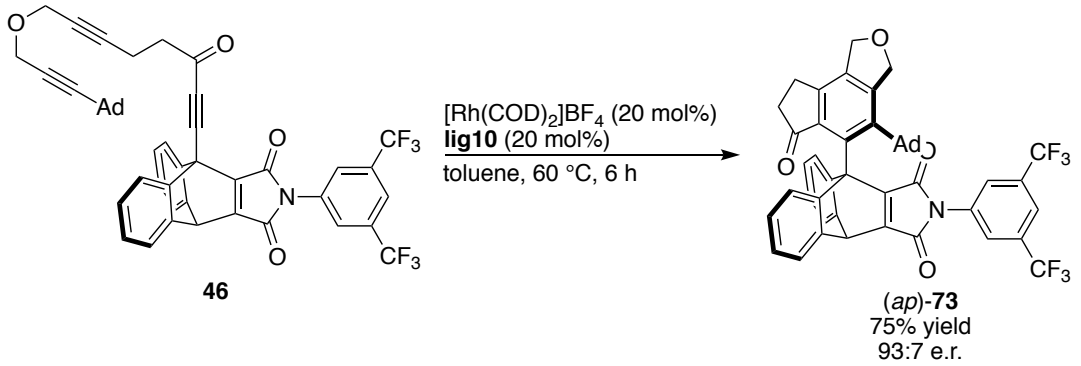
Entry[a]	Precatalyst	Ratio (*ap*)-**73** / dimers	Yield	e.r.
1	$[Rh(COD)_2]BF_4$	1:0.35	-	91:9
2	$[Rh(COD)_2]OTf$	No dimer	33%	78:22
3	$[Rh(COD)_2]B_{Ar}F$	-	-	-
4	$[Rh(COD)_2]SbF_6$	-	-	-

[a] Performed with 15.0 µmol of **64** at a concentration of 3.00 $mmolL^{-1}$.

4.8.4. Examination of Different Reaction Temperatures

The high configurational stability of the Csp^2-Csp^3 atropisomer (*ap*)-**73** allowed to further increase the reaction temperature to examine the effect on the yield and selectivity. Even less dimers were formed at a temperature of 60 °C and a ratio of 1:0.16 of (*ap*)-**73** to dimers was observed. Additionally, adding of the substrate **64** in three portions over 1.5 hours was found to be beneficial and the (*ap*)-**73** was isolated after six hours in good yield of 75% and a high enantiomeric ratio of 93:7 (Scheme 72). At a slightly elevated temperature of 65 °C, the catalyst loading could be lowered by half (to 10 mol%) and the (*ap*)-**73** was obtained in a slightly decreased yield of 55%

and and e.r. of 91:9. Further increase of the reaction temperature resulted in lower selectivities and decreased yields due to side product formation.



Scheme 72: Optimized reaction condition of the [2+2+2]-cyclotrimerization for the (*ap*)-**73**.

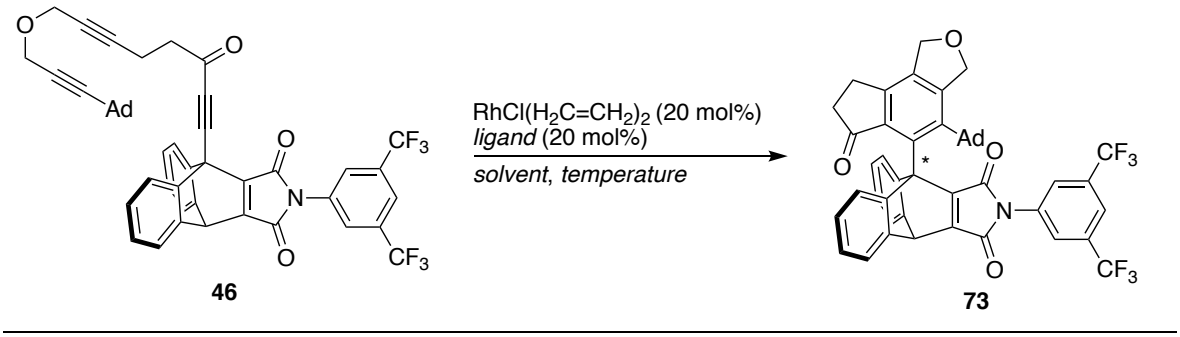
Detailed examination of ligands, precatalysts, solvents and reaction temperatures allowed to optimize the [2+2+2]-cyclotrimerization reaction to an astonishingly selective process for the (*ap*)-**73** which was isolated in 75% yield and an excellent enantioselectivity of 93:7.

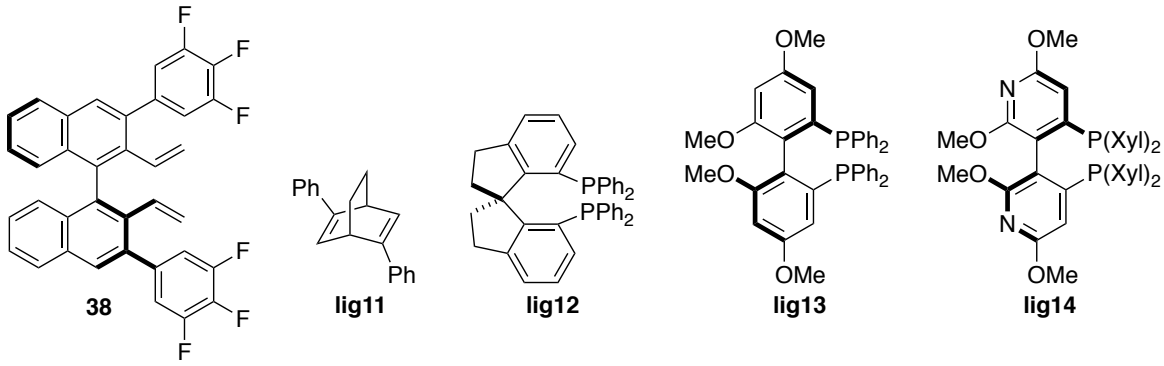
4.9. Preliminary Results for a Second Stereoisomer

During the optimization of the [2+2+2]-cyclotrimerization towards the (*ap*)-**73**, we detected a second stereoisomer of **73** by using the diene ligand **38** (section 3.6.) in combination with the rhodium catalyst $RhCl(H_2C{=}CH_2)_2$. A first promising yield of 10% together with an enantiomeric ratio of 59:51 was obtained (Table 11, Entry1). Encouraged by this exciting result, we initiated an optimization to this second stereoisomer. Related to the diene ligand **38**, the commercially available diene **lig11** [152] was explored with $RhCl(H_2C{=}CH_2)_2$ as a rhodium precursor. A low conversion of only 12% was observed yielding the (*ap*)-**73** and the desired stereoisomer in a 1:1 ratio, but an increase in enantioselectivity to 74:26 for the desired conformer was measured (Table 11, Entry 2). The enantioselectivity was even more increased to 85:15 by using an excess of the ligand. However, the conversion remained low and the desired conformer was obtained as a 1:1 mixture with the (*ap*)-**73** (Table 11, Entry 3). Changing the solvent to toluene did not lead to any formation of the preferred stereoisomer (Table 11, Entry 4). The second stereoisomer was also detected at elevated temperatures of 115 °C with the spiro ligand **lig12** in combination with the cationic rhodium. It thereby remained elusive whether the desired conformer is formed during the reaction or results from the rotation around the restricted bond. Even though full conversion of **64** was achieved, the conditions strongly favored the formation of the (*ap*)-**73** and the preferred conformer was obtained

in poor yields and an enantioselectivity of 74:26 (Table 11, Entry 5). A higher conversion of 40% compared to the diene ligand **lig11** was found with the Garphos ligand **lig13**, but again the (*ap*)-**73** was favorably formed (Table 11, Entry 6).

Table 11: Preliminary optimization for a second stereoisomer of **73**.





Entry[a]	Ligand	Solvent	Conversion (Ratio (*ap*)-**73** to other conformer	**e.r.** for other conformer
1[b]	**38**	DCE	20% (1:1)	59:41
2[b]	**lig11**	DCE	12% (1:1)	74:26
3[b,c]	**lig11**	DCE	10% (1:1)	85:15
4[d]	**lig11**	toluene	-	-
5[e]	**lig12**	toluene	100% (3:1)	74:26
6[d]	**lig13**	toluene	40% (2:1)	70:30
7[c,f]	**lig14**	toluene	100%, traces of product	65:35

[a] Performed with 15.0 µmol of **64** at a concentration of 3.00 mmolL^{-1}; [b] Performed at 50 °C; [c] Performed with a catalyst to ligand ratio of 1:2.5; [d] Performed at 80 °C; [e] Performed with [Rh(COD$_2$)]BF$_4$ at 115 °C; [f] Performed with LiCl as additive.

The structurally related bipyridine ligand **lig14** and LiCl as additive fully converted the substrate **64**, however, the desired stereoisomer was formed in a low yield as a 1:1 mixture with the (*ap*)-**73** and a poor enantioselectivity of 65:35 (Table 11, Entry 7). The low yields obtained in the conducted reactions so far inhibited a detailed analysis of the second stereoisomer and the configuration is

still unknown. The investigations towards the second conformer of the [2+2+2]-cyclotrimerization are currently conducted by X. Wu and R. Beaud (see Outlook).

4.10. Summary

The [2+2+2]-cyclotrimerization was identified as a suitable reaction for the preparation of Csp^2-Csp^3 atropisomers. Thereby, tethered alkynes attached to an ethenoanthracene structure was found to be an ideal substrate scaffold, which allows to synthesize all three possible diastereoisomers of a Csp^2-Csp^3 atropisomeric product possessing a low barrier to rotation. Investigations of the rotational profile enabled to design and synthesize a second-generation substrate bearing a keto function in the alkyne chain exhibiting a significant contribution to increase the configurational stability of the rotationally restricted axis. A rhodium catalyzed [2+2+2]-cyclotrimerization of this new substrate resulted in the isolation and characterization of the enantioenriched (*ap*)-isomer **73** as a proof of concept for the first stereoselective synthesis of Csp^2-Csp^3 atropisomer from substrates which do not possess s stereogenic element. Remarkable configurational stability was found for the (*ap*)-**73** and no isomerization was observed at temperatures up to 100 °C. Furthermore, X-ray analysis revealed that the (*ap*)-**73** is prone to undergo a light-induced, stereospecific di-π-methane rearrangement to a semi bullvalene core. The [2+2+2]-cyclotrimerization was further optimized and the (*ap*)-**73** was prepared in good yields up to 75% and high atroposelectivities up to 93:7 by the combination of a cationic rhodium precatalyst and a spiro-biindene ligand. As a preliminary result, a second stereoisomer of **73** was obtained with enantioselectivities of up to 85:15 by using a rhodium catalyst in combination with a chiral diene ligand.

4.11. Outlook

This project is continued by X. Wu and R. Beaud with the exploration of different substrates in order to examine the scope and limitations of the developed methodology. Modifications of the substrates are planned in the aryl unit of the maleimide part in order to explore the influence of the electronic as well as steric influence on cyclotrimerization reaction. Especially exciting is the 4-bromo benzene that potentially allows further derivatization of this position through cross-coupling reactions or 3,4,5-trimethoxybenzene with inverse electronic properties compared to the electron deficient bis-(trifluoromethyl)benzene (Figure 21, a).

Furthermore, different tether moieties between the second and the third alkyne of the substrate will be examined to evaluate the influence on the reactivity in the cyclotrimerization reaction. The diethyl malonate, the N-tosyl as well as the dimethoxypropane are envisioned to be explored (Figure 21, b).

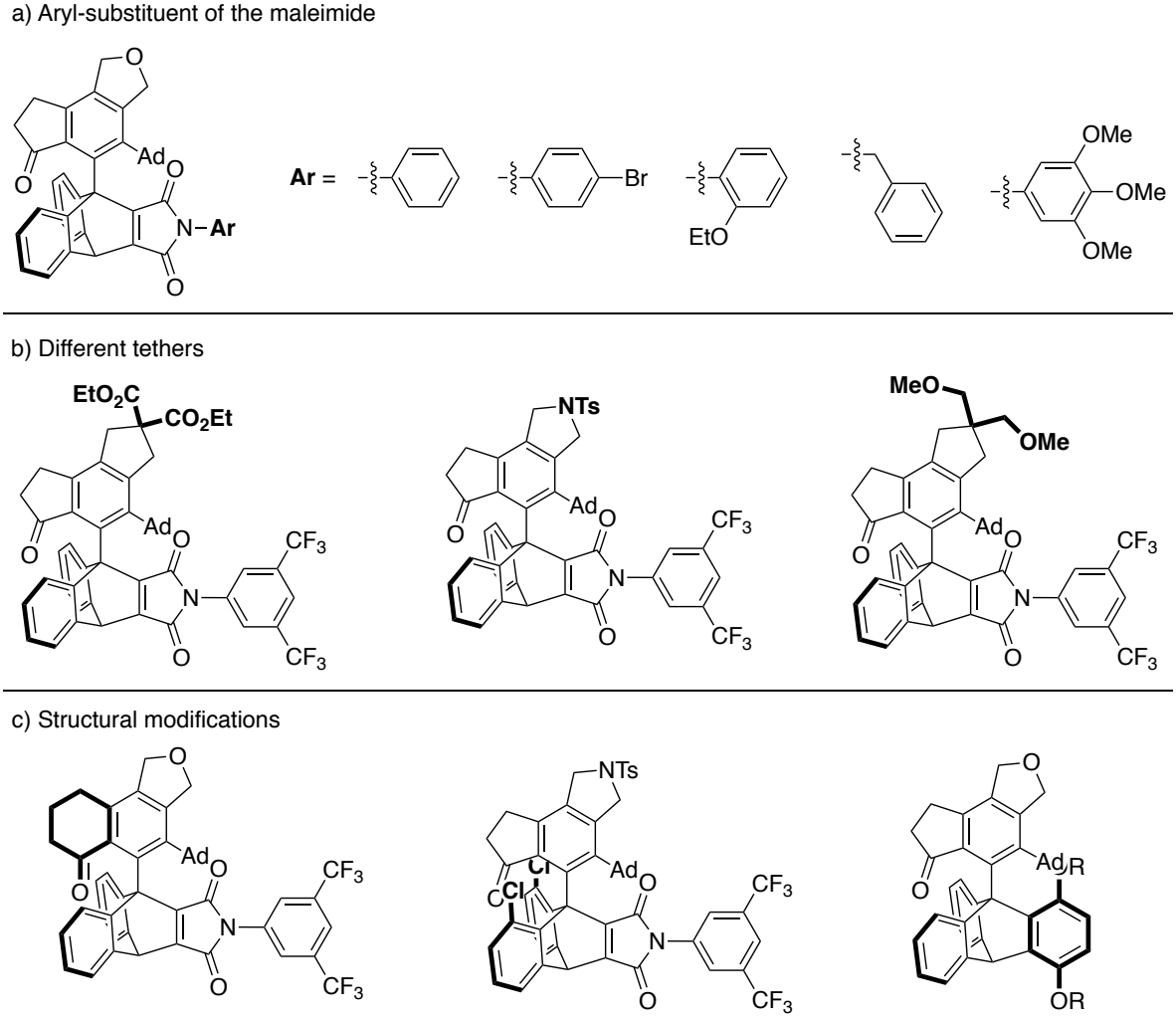


Figure 21: Intended substrates to examine the scope and limitations of the developed [2+2+2]-cyclotrimerization to stereoselectively prepare Csp^2-Csp^3-atropismers.

Finally, more significant structural modifications are intended to be evaluated in order to explore the influence of sterics in close proximity to the rotationally restricted axis. One consideration is to expand the tether between two alkynes by one carbon in order to obtain a cyclohexanone instead of a cyclopentanone ring. The angle of the keto functionality pointing into the cavity would thereby be different. The effect of a ground state destabilization is intended to be examined with the introduction of chlorine substituents in the 1-position of the benzene units of the ethenoanthracene.

Furthermore, the importance of the maleimide part of the Csp^2-Csp^3 atropisomer will be examined with the triptycene analogue derived from a Diels-Alder reaction with benzoquinone (Figure 21, c).

Examination of the different substrates will give a representative illustration of the possibilities and limitations of the developed [2+2+2]-cyclotrimerization reaction. The configurational stabilities of the products might allow to predict the influence of the substituents on the rotational barrier. Ultimately, one of these substrates might selectively provide one or even both of the other two possible stereoisomers resulting from the restricted rotation about the Csp^2-Csp^3 single bond.

5. Conclusion

This thesis describes the development of two distinct catalytic methodologies both addressing the challenge to access sterically demanding rotationally restricted products. The noncanonical polyketide cyclization was developed to stereoselectively prepare tetra-*ortho*-substituted binaphthalenes, as fully substituted Csp^2-Csp^2 axis. While the four *ortho*-substituents result in high configurational stability of the axis, it also exhibits considerable steric congestion during their synthesis. On the other hand, the [2+2+2]-cyclotrimerization was established for the stereoselective preparation of Csp^2-Csp^3 atropisomers which typically have a low rotational barrier. Increase of the steric demand may lead to an increased ground state energy and thereby a lower configurational stability of the products. Thus, careful selection of substituents is crucial to prepare configurationally stable Csp^2-Csp^3 atropisomers and to furthermore maintain the reactivity of the substrates.

Secondary amines were found to efficiently catalyze the noncanonical polyketide cyclization mimicking the polyketide synthases in the biosynthesis of aromatic polyketides. Thereby, tetra-*ortho*-substituted binaphthalenes were obtained in good yields and high atroposelectivities. A notable four-fold ozonolysis enabled the conversion of the biindene precursors into the noncanonical hexa-carbonyl substrate for the aldol methodology. The ozonolysis precursors were readily accessible either through an oxidative dimerization for symmetric biindenes or through a Suzuki cross-coupling reaction for unsymmetric biindenes. Taking advantage of the hydroxy functionalities in the 3,3'-position of the prepared products, straight-forward syntheses of a diene ligand, a [5]helicene and the Maruoka catalyst were achieved, demonstrating the utility of the obtained binaphthalene scaffold.

A substrate consisting of a trialkyne chain attached to an ethenoanthracene was a suitable starting point to investigate the [2+2+2]-cyclotrimerization for the stereoselective preparation of Csp^2-Csp^3-atropisomers. With an adamantyl group in terminal position, all three diastereoisomers of the rotationally restricted Csp^2-Csp^3 product were observed, albeit the interconversion occurred rapidly and thereby prohibited the development of a stereoselective method. Detailed analysis of the bond

rotational profile revealed the essential incorporation of a ketone functionality into the substrate, finally leading to cyclotrimerization products possessing a Csp^2-Csp^3 axis, which were configurationally stable up to 100 °C. The second-generation substrates enabled to establish the first stereoselective method for the preparation of Csp^2-Csp^3-atropisomers with the restricted axis as the only stereogenic element. An unexpected stereospecific di-π-methane rearrangement of the (*ap*)-conformer was detected during crystal structure analysis. Examination of conditions revealed the utility of a cationic rhodium catalyst combined with a spiro ligand, enabling to prepare the (*ap*)-conformer in a good yield of 75% and a high atroposelectivity of 93:7. As a preliminary result, a second diastereoisomer was accessed in an enantioselectivity of up to 85:15.

6. Supporting Information

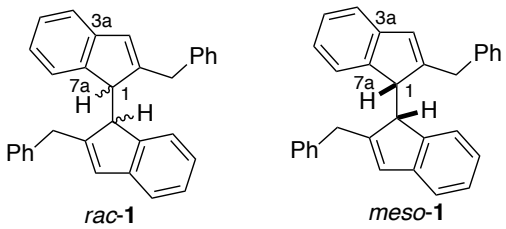
6.1. 1. General Information

All chemicals were reagent grade and used as supplied unless stated otherwise. 2-Ethyl-1*H*-indene (**4b**),[153] 2-benzyl-1*H*-indene (**4a**),[94] 5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (**18b**),[116] and 4,7-difluoro-2,3-dihydro-1*H*-inden-1-one (**18c**),[117] 5,6-dimethyl-2,3-dihydro-1*H*-inden-1-one (**18d**),[154] 2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (**18i**),[155] 4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (**18j**),[156] 1-(2,2-bibromovinyl)adamantane (**70**),[144] 9-(2,2-dibromovinyl)anthracene (**57**)[157] were prepared according to a literature known procedure. The $TiCl_4$ solution (1.00 $molL^{-1}$ solution in CH_2Cl_2) was prepared with pure $TiCl_4$ from *Acros* (No. 197231000) and dry CH_2Cl_2 from *Acros* (No. 348465000). Ozone was generated with an ozone generator *BMT 802 N* from *BMT Messtechnik GmbH* and oxygen from *Pangas* (quality = 5.0). The concentration of *n*-BuLi from *Acros* (ACR18127-1000) was determined by titration.[158] All reactions were carried out in oven dried glassware and under an argon atmosphere. All used solvents were ACS grade. Extracts were dried over technical grade Na_2SO_4. Analytical and preparative thin layer chromatography (TLC) was performed on pre-coated *Merck* silica gel 60 F_{254} plates (0.25 mm) and visualized by UV (254 nm) or $KMnO_4$ with heating. Column chromatography was carried out on *Silicycle* SiliaFlash P60 (230–400 mesh). Concentration *in vacuo* was performed by rotary evaporation to ~10 mbar at 40 °C. Final products were dried at ~10^{-1} mbar at RT. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *BrukerAvance III* (600 MHz), *BrukerAdvance III* (500 MHz) and *BrukerAvance* (400 MHz) at 298 K in $CDCl_3$, CD_2Cl_2 or $(CD_3)_2SO$ supplied by *Cambridge Isotope Laboratories*. Chemical shifts (δ) are reported in ppm relative to TMS (0.00 ppm) for the ^{1}H NMR and to $CDCl_3$ (77.16 ppm) for ^{13}C NMR. Spectra measured in CD_2Cl_2 and $(CD_3)_2SO$ were relative to the solvent peak (5.30 ppm/53.84 ppm and 2.50 ppm/39.52 ppm). The multiplicities are reported in Hz as: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting points (m.p.) were measured on a *Büchi B-565* melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on an ATR *Varian Scimitar 800* FT-IR spectrometer and are reported in cm^{-1}. Optical rotations were obtained at RT on a *JASCO P-2000* polarimeter using a 1.00 mL cell

with a length of 100 mm; the concentrations are reported in g/100 mL. High-resolution ESI mass spectrometry (HRMS-ESI) was performed by Dr. Heinz Nadig, Dr. Michael Pfeffer and Sylvie Mittelheisser of the University of Basel on a *Bruker maXis 4G* QTOF ESI mass spectrometer.

6.2. 1*H*,1*H*'-Biindenes and 3*H*,3*H*'-Biindenes

6.2.1. 2,2'-Dibenzyl-1*H*,1'*H*-1,1'-biindene (1)



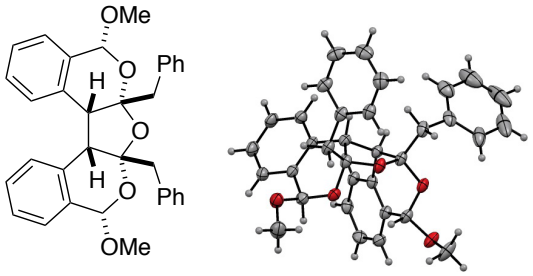
2-Benzyl-1*H*-indene (**4a**, 1.94 g, 9.42 mmol, 2.0 eq) was dissolved in dry Et_2O (8.0 mL). After cooling to –78 °C, *n*-BuLi (1.24 $molL^{-1}$ in hexanes, 8.35 mL, 10.4 mmol, 1.1 eq) was added dropwise and the yellow suspension was stirred at –78 °C for 2 h. After dilution with Et_2O (10 mL), $CuCl_2$ (1.52 g, 11.3 mmol, 1.2 eq) was added and the suspension was warmed up to RT. After 18 h at RT the mixture was diluted with Et_2O (100 mL) and was decanted. The solids were washed with Et_2O (50 mL) and the mixture was decanted again. The org. layer was washed with aq. HCl (1.00 $molL^{-1}$, 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) to yield *meso*-**1** as a slight yellow solid (485 mg, 25%, m.p. = 140–147 °C) and *rac*-**1** as a slight yellow solid (435 mg, 22%, m.p. = 157–161 °C) together with a mixed fraction of both (357 mg, 18%).

meso-2,2'-Dibenzyl-1*H*,1'*H*-1,1'-biindene (**1**): R_f 0.27 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 2897w, 1603w, 1460m, 1308w, 1073w, 1029w, 907w, 850w, 752s, 700s; ^{1}H NMR (500 MHz, $CDCl_3$, as a 1:1 mixture of rotamers) δ = 7.37–7.10 (14H, m), 6.83 (2H, d, *J* 7.2), 6.75 (1H, t, *J* 7.5), 6.60 (1H, s), 6.10 (1H, s), 5.95 (1H, d, *J* 7.5), 4.05 (1H, s), 4.00 (1H, s), 3.86 (1H, d, *J* 15.8), 3.51 (1H, d, *J* 15.7), 3.24 (1H, d, *J* 16.8), 3.01 (1H, d, *J* 16.5); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.7, 150.9, 147.2, 144.7, 144.0, 139.9, 129.2, 129.2, 128.9, 128.9, 128.4, 127.1, 126.9, 126.6, 126.1, 124.6, 124.3, 122.9, 122.8, 120.5, 51.9, 48.7, 36.5, 36.3;

rac-2,2'-Dibenzyl-1*H*,1'*H*-1,1'-biindene (**1**): R_f 0.18 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 2896w, 1602w, 1458m, 1179w, 1073w, 1028w, 908w, 749s, 700s; ^{1}H NMR (500 MHz, $CDCl_3$, as

a 1:1 mixture of rotamers) δ = 7.41 (1H, d, *J* 7.7), 7.33–7.19 (7H, m), 7.17–7.10 (4H, m), 7.07 (1H, d, *J* 7.9), 7.01–6.92 (2H, m), 6.78 (1H, t, *J* 7.4), 6.71 (2H, d, *J* 6.9), 6.61 (1H, s), 6.31 (1H, s), 4.10 (1H, s), 4.06 (1H, d, *J* 15.8), 3.88 (1H, s), 3.79 (1H, d, *J* 15.6), 3.00 (1H, d, *J* 16.6), 2.63 (1H, d, *J* 16.6); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 152.5, 150.5, 146.3, 144.5, 144.2, 143.5, 139.7, 139.7, 129.5, 129.1, 129.1, 128.8, 128.5, 128.1, 127.1, 126.7, 126.5, 126.0, 125.0, 123.8, 123.1, 122.4, 120.3, 120.3, 51.2, 49.1, 36.5;

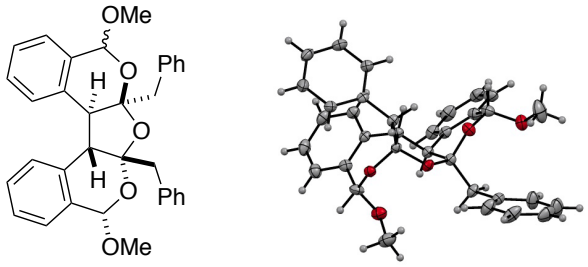
6.2.2. *meso*-6a,7a-Dibenzyl-5,9-dimethoxy-6a,7a,13b,13c-tetrahydro-5*H*,9*H*-furo[2,3-*c*:5,4-*c′*]diisochromene (*meso*-5)



meso–**5**

meso-2,2'-Dibenzyl-1*H*,1'*H*-1,1'-biindene (*meso*-**1**, 1.01 g, 2.46 mmol. 1.0 eq) was dissolved in a mixture of CH_2Cl_2 (60 mL) and MeOH (30 mL). At –78 °C, an O_2/O_3 mixture (0.2 L/min, voltage = 9) was bubbled through the solution until a slightly blue coloration was observed. The blue mixture was purged with Argon until the blue coloration vanished, DMS (18.0 mL, 246 mmol, 100 eq) was added and the mixture was warmed to RT. After stirring at RT for 4 h, the mixture was diluted with H_2O (100 mL) and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 1:10) to yield the title compound *meso*-**5** as a white solid (643 mg, 50%, m.p. = 128–133 °C): R_f 0.60 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3031w, 2928w, 1605w, 1495w, 1454m, 1351m, 1217m, 1086s, 1014s, 917m, 852w, 752s, 700s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29–7.20 (12H, m), 7.18 (2H, d, *J* 7.4), 7.12 (2H, ddd, *J* 7.6, 7.4, 1.2), 7.00 (2H, ddd, *J* 7.6 7.4, 1.3), 6.58 (2H, d, *J* 7.6), 5.25 (2H, s), 3.48 (6H, s), 3.43 (2H, s), 3.07 (2H, d, *J* 14.2), 2.91 (2H, d, *J* 14.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 136.4, 135.1, 131.9, 130.9, 129.1, 128.1, 127.4, 126.9, 126.7, 125.4, 106.5, 97.3, 55.7, 46.2, 44.5; ESI-MS: m/z calc. for $C_{34}H_{32}O_5Na^+$ 543.2142 found 543.2150 [M+Na^+]; Crystals suitable for X-ray crystallographic analysis were obtained by diffusion of *n*-pentane into a solution of *meso*-**5** in $CDCl_3$.

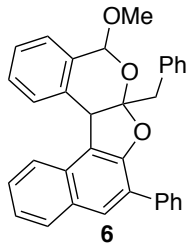
6.2.3. *rac*-6a,7a-Dibenzyl-5,9-dimethoxy-6a,7a,13b,13c-tetrahydro-5*H*,9*H*-furo[2,3-c:5,4-c']diisochromene (*rac*-5)



rac–**5**

rac-2,2'-Dibenzyl-1*H*,1'*H*-1,1'-biindene (*rac*-**1**, 233 mg, 567 µmol. 1.0 eq) was dissolved in a mixture of CH_2Cl_2 (20 mL) and MeOH (10 mL). At –78 °C, an O_2/O_3 mixture (0.2 L/min, voltage = 9) was bubbled through the solution until a slightly blue coloration was observed. The blue mixture was purged with Argon until the blue coloration vanished and DMS (4.14 mL, 56.7 mmol, 100 eq) was added and the mixture was warmed to RT. After stirring at RT for 4 h, the mixture was diluted with H_2O (50 mL) and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 1:10) to yield the title compound *rac*-**5** as a white solid (116 mg, 39%, m.p. = 146–150 °C): R_f 0.63 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3031w, 2932w, 1495w, 1455m, 1360m, 1228m, 1082s, 1015m, 952s, 757s, 701s; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoiosmers) δ = 7.38 (1.7H, d, *J* 7.7), 7.36–7.32 (1.3H, m), 7.28–7.22 (4.3H, m), 7.19–6.95 (17H, m), 6.46 (1H, t, *J* 7.7), 6.40 (0.3H, d, *J* 7.5), 6.37 (1.5H, dd, *J* 7.7, 0.8), 5.71 (0.5H, s), 5.66 (0.3H, s), 3.65–3.63 (1.3H, m), 3.58 (4.5H, s), 3.56 (0.3H, s), 3.54 (0.3H, s), 3.51 (1.5H, s), 3.41 (0.6H, s), 3.38 (0.8H, s), 3.35 (1.5H, s), 3.33 (0.3H, s), 3.30 (0.4H, s), 3.23–3.11 (3H, m), 3.06 (0.3H, s), 3.04 (0.3H, s), 3.01 (0.2H, s), 2.98 (0.2H, s), 2.91 (1.5H, s); ESI-MS: m/z calc. for $C_{34}H_{32}O_5Na^+$ 543.2142 found 543.2151 [M+Na^+]; Crystals suitable for X-ray crystallographic analysis were obtained by diffusion of *n*-pentane into a solution of *rac*-**5** in $CDCl_3$.

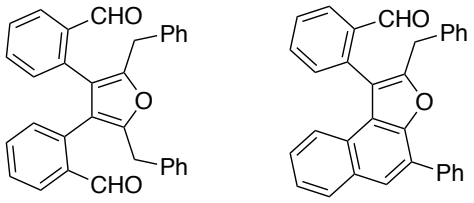
6.2.4. 6a-Benzyl-5-methoxy-8-phenyl-6a,13c-dihydro-5*H*-naphtho[1',2':4,5]-furo[2,3-*c*]isochromene (6)



6

meso-6a,7a-Dibenzyl-5,9-dimethoxy-6a,7a,13b,13c-tetrahydro-5*H*,9*H*-furo[2,3-*c*:5,4-*c'*]diiso-chromene (*meso*-**5**, 10.0 mg, 19.2 μmol, 1.0 eq) was dissolved in $CDCl_3$ (1.0 mL). L-Alanine·TFA (710 μg, 3.84 μmol, 20 mol%) was added and the mixture was stirred at RT for 15 h before the mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:3 to 1:1) to yield the title compound **6** as a colorless oil (0.9 mg, 10%): R_f 0.46 (Et_2O/*n*-pentane, 1:19); ν_{max} (neat): 3059w, 3031w, 2956m, 2921s, 2852m, 1496m, 1455m, 1431m, 1371m, 1275m, 1214m, 1085s, 1050m, 1009s, 977s, 907m, 760s, 698s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.88–7.83 (2H, m), 7.81 (1H, d, *J* 8.4), 7.77 (1H, s), 7.45 (1H, d, *J* 7.8), 7.67 (1H, d, *J* 7.4), 7.52–7.47 (2H, m), 7.42–7.36 (2H, m), 7.32–7.29 (2H, m), 7.25–7.22 (2H, m), 7.21–7.16 (3H, m), 7.16–7.13 (2H, m), 5.53 (1H, s), 5.01 (1H, s), 3.41 (1H, d, *J* 14.0), 3.32 (1H, d, *J* 14.0), 3.14 (3H, s); ESI-MS: m/z calc. for $C_{33}H_{26}O_3Na^+$ 493.1774 found 493.1782 [$M+Na^+$].

6.2.5. 2,2'-(2,5-Dibenzylfuran-3,4-diyl)dibenzaldehyde (7) and 2-(2-benzyl-4-phenylnaphtho[2,1-*b*]furan-1-yl)benzaldehyde (8)



7 **8**

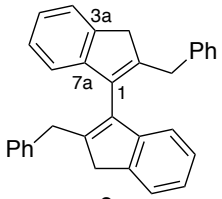
meso-6a,7a-Dibenzyl-5,9-dimethoxy-6a,7a,13b,13c-tetrahydro-5*H*,9*H*-furo[2,3-*c*:5,4-*c'*]diiso-chromene (*meso*-**5**, 10.0 mg, 19.2 μmol, 1.0 eq) was dissolved in $CDCl_3$ (2.0 mL) and a solution of $NaB_{Ar}F$ (19.2 mmolL^{-1} in D_2O, 100 μL , 0.192 μmol, 0.1 eq) added followed by the addition of L-alanine (170 μg, 1.91 μmol, 10 mol%). After stirring the mixture at RT for 18 h the mixture was

concentrated *in vacuo* and the two products were separated by preparative TLC (Et_2O/*n*-pentane, 1:5) to yield **7** as a colourless oil (2.3 mg, 26%) and **8** as a slight yellow oil (1.4 mg, 17%).

2,2'-(2,5-Dibenzylfuran-3,4-diyl)dibenzaldehyde (**7**): R_f 0.31 (Et_2O/*n*-pentane, 1:10); ν_{max} (neat): 3060w, 3031w, 1695s, 1595m, 1496m, 1453m, 1381m, 1266w, 1197m, 1085m, 1008m, 986m, 767s, 735s, 698s; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.90 (1H, d, *J* 0.8), 8.16 (1H, dd, *J* 7.7, 1.2), 7.98–7.92 (3H, m), 7.87 (1H, s), 7.76 (1H, ddd, *J* 7.6, 7.5, 1.5), 7.70–7.76 (1H, m), 7.58–7.51 (3H, m), 7.48–7.43 (1H, m), 7.42–7.37 (1H, m), 7.36–7.32 (1H, m), 7.25–7.17 (4H, m), 7.16–7.12 (2H, m), 4.10–3.98 (2H, m); ESI-MS: m/z calc. for $C_{32}H_{22}O_2Na^+$ 461.1512 found 461.1516 [$M+Na^+$].

2-(2-Benzyl-4-phenylnaphtho[2,1-*b*]furan-1-yl)benzaldehyde (**8**): R_f 0.48 (Et_2O/*n*-pentane, 1:5); ν_{max} (neat): 3063w, 3030w, 2925w, 2847w, 2745w, 1695s, 1597m, 1495w, 1454w, 1264w, 1197m, 992w, 825w, 768m, 732m, 701m; ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ = 9.92 (0.6H, d, *J* 0.6), 9.80 (1.2H, d, *J* 0.7), 7.81 (0.6H, dd, *J* 7.8, 1.2), 7.73 (1.2H, dd, *J* 7.8, 1.1), 7.50 (1.4H, ddd, *J* 7.6, 7.5, 1.4), 7.44 (0.7H, ddd, *J* 7.6, 7.5, 1.4), 7.38–7.33 (2H, m), 7.28–7.16 (8H, m), 7.12–7.05 (4H, m), 4.02–3.83 (4H, m); ESI-MS: m/z calc. for $C_{32}H_{25}O_3^+$ 457.1798 found 457.1798 [$M+H^+$].

6.2.6. 2,2'-Dibenzyl-3*H*,3'*H*-1,1'-biindene (9a)

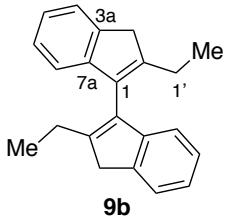


9a

A Schlenk-tube (100 mL) was charged with *n*-BuLi (1.35 $molL^{-1}$ in hexanes, 11.5 mL, 15.4 mmol, 1.1 eq). After cooling to –78 °C, a solution of 2-benzyl-1*H*-indene (**4a**, 2.89 g, 12.0 mmol, 1.0 eq) in Et_2O (30 mL) was added dropwise. The slightly yellow mixture was stirred at –78 °C for 1.5 h. After 30 min, a white precipitation formed. $CuCl_2$ (2.26 g, 16.8 mmol, 1.2 eq) was added in one portion and the black mixture was warmed up to RT. After stirring at RT for 16 h, Et_2O (3x 50 mL) was added in portions and the suspension was decanted each time. The combined supernatants were washed with aq. sat. NH_4Cl (2x 100 mL) and brine (50 mL). Each aq. layer was reextracted with Et_2O (50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (40 mL) and pyrrolidine (5.0 mL) was added.

The green mixture was stirred at RT for 2.5 h and was washed with aq. HCl (1.00 molL^{-1}, 2x 70 mL) and brine (100 mL). The aq. layers were reextracted with CH_2Cl_2 (2x 50 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:19 to 1:9) to yield the title compound **9a** as a slightly yellow solid (2.46 g, 86%, m.p. = 124–130 °C): R_f 0.39 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 1603w, 1493w, 1459m, 1392w, 907m, 723s, 698s, 649w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 (2H, d, ^3J 7.2, C4*H*), 7.24–7.17 (6H, m), 7.16–7.09 (10H, m), 3.84 (2H, d, ^1J 15.1, C3*H*), 3.70 (2H, d, ^1J 15.0, C3*H*), 3.43 (4H, s, CH_2Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.1, 145.9, 143.0, 140.5, 133.8, 128.9, 128.6, 126.4, 126.2, 124.5, 123.6 (*C*4), 120.4, 40.7 (*C*H_2Ph), 36.3 (*C*3).

6.2.7. 2,2'-Diethyl-3*H*,3'*H*-1,1'-biindene (9b)

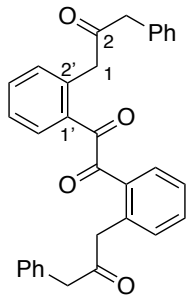


9b

A Schlenk-tube (100 mL) was charged with *n*-BuLi (1.36 molL^{-1} in hexanes, 9.80 mL, 13.3 mmol, 1.1 eq). After cooling to –78 °C, a solution of 2-ethyl-1*H*-indene (**4b**, 1.75 g, 12.1 mmol, 1.0 eq) in Et_2O (20 mL) was added dropwise. The slightly yellow mixture was stirred at –78 °C for 1 h before $CuCl_2$ (1.95 g, 14.5 mmol, 1.2 eq) was added in one portion. The suspension was warmed to RT and the brown mixture was stirred at RT 16 h before Et_2O (3x 50 mL) was added in portions and the suspension was decanted each time. The combined supernatants were washed with aq. HCl (1.00 molL^{-1}, 100 mL), aq. sat. NH_4Cl (100 mL) and brine (50 mL). Each aq. layer was reextracted with Et_2O (50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (50 mL) and pyrrolidine (5.0 mL) was added. The yellow mixture was stirred at RT for 2.5 h and the mixture was washed with aq. HCl (1.00 molL^{-1}, 2x 50 mL). The aq. layer was reextracted with CH_2Cl_2 (50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) to yield the title compound **9b** as a slightly yellow solid (1.42 g, 82%, m.p. = 91–94 °C): R_f 0.57 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3067w, 3019w, 2965m, 2933m, 2877m, 1604w, 1461s, 1391m, 1018w, 760s, 722s; ^{1}H NMR (500 MHz,

$CDCl_3$) δ = 7.48–7.43 (2H, m, C4*H*), 7.18–7.11 (4H, m, C5*H*/C6*H*), 7.00–6.96 (2H, m, C7*H*), 3.58–3.47 (4H, m, C3*H*), 2.44–2.34 (4H, m, C1'*H*), 1.11 (6H, t, ^3J 7.6, C2'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.7 (*C*2), 146.6 (*C*7a), 142.7 (*C*3a), 132.2 (*C*1), 126.2 (*C*6), 123.9 (*C*5), 123.5 (*C*4), 120.0 (*C*7), 40.0 (*C*3), 22.9 (*C*1'), 14.4 (*C*2').

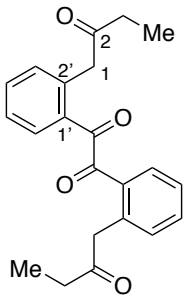
6.2.8. 1,2-Bis(2-(2-oxo-3-phenylpropyl)phenyl)ethane-1,2-dione (10a)



10a

A two-necked flask (25 mL) equipped with a glass stopper and a silicon septum with argon balloon was charged with 2,2'-dibenzyl-3*H*,3'*H*-1,1'-biindene (**9a**, 200 mg, 487 µmol, 1.0 eq) dissolved in CH_2Cl_2 (15 mL). After cooling to –78 °C, the stopper was replaced with a drying tube charged with $CaCl_2$ and the septum was replaced with an ozone inlet. An O_2/O_3 mixture (0.2 L/min, voltage = 9) was bubbled through the solution until a slightly blue coloration was observed. The ozone inlet was replaced with a septum and argon was bubbled through the solution until the blue coloration disappeared. PPh_3 (639 mg, 2.43 mmol, 5.0 eq) was added in one portion and the mixture was warmed up to RT over 2 h. The mixture was concentrated *in vacuo* and purified by column chromatography (Et_2O/*n*-pentane, 1:2) to yield the title compound **10a** as a yellow oil (136 mg, 58%): R_f 0.40 (Et_2O/*n*-pentane, 1:2); ν_{max} (neat): 3029w, 1719s, 1674s, 1573m, 1334m, 1206m, 1061m, 902w, 738m, 700m, 649m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (2H, dd, ^3J 7.8, ^4J 1.3, C6'*H*), 7.48 (2H, ddd, ^3J 7.5, 7.5, ^4J 1.3, C4'*H*), 7.35–7.22 (12H, m, C5'*H*, Ph*H*), 7.15 (2H, dd, ^3J 7.6, ^4J 0.9, C3'*H*), 4.16 (4H, s, C1*H*), 3.96 (4H, s, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ =204.9 (*C*2), 196.7 (Ar*C*O), 137.4 (*C*2'), 134.5, 134.5 (*C*6'), 134.3 (*C*4'), 133.5 (*C*3'), 131.0 (*C*1'), 129.8, 128.7, 127.7 (*C*5'), 127.0, 50.3 (*C*3), 48.3 (*C*1); ESI-MS: m/z calc. for $C_{32}H_{27}O_4^+$ 475.1904 found 475.1903 [$M+H^+$].

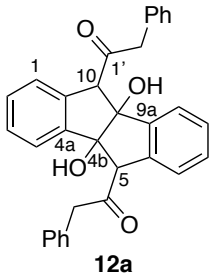
6.2.9. 1,2-Bis(2-(2-oxobutyl)phenyl)ethane-1,2-dione (10b)



10b

A two-necked flask (50 mL) equipped with a glass stopper and a silicon septum with an argon balloon was charged with 2,2'-diethyl-3*H*,3'*H*-1,1'-biindene (**9b**, 215 mg, 750 µmol, 1.0 eq) dissolved in CH_2Cl_2 (30 mL). After cooling to –78 °C, the stopper was replaced with a drying tube charged with $CaCl_2$ and the septum was replaced with an ozone inlet. An O_2/O_3 mixture (0.2 L/min, voltage = 9) was bubbled through the solution for 2.0 min and a slightly blue coloration was observed. The ozone inlet was replaced with the septum and argon was bubbled through the solution until the blue coloration disappeared. PPh_3 (787 mg, 3.0 mmol, 4.0 eq) was added in one portion and the mixture was warmed to RT. After stirring at RT for 14 h, the mixture was concentrated *in vacuo* and purified by column chromatography (Et_2O/*n*-pentane, 1:4 to 1:2 to 1:1) to yield the title compound **10b** as a slightly yellow oil (128 mg, 49%): R_f 0.19 (Et_2O/*n*-pentane, 1:2); ν_{max} (neat): 2978w, 1716s, 1674s, 1601w, 1524m, 1318m, 1207s, 1109m, 743m, 653m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66 (2H, dd, ^3J 7.8, ^4J 1.3, C6'*H*), 7.56 (2H, ddd, ^3J 7.5, 7.5, ^4J 1.3, C4'*H*), 7.39 (2H, ddd, ^3J 7.7, 7.6, ^4J 1.2, C5'*H*), 7.28–7.25 (2H, m, C3'*H*), 4.19 (4H, s, C1*H*), 2.69 (4H, q, ^3J 7.4, C3*H*), 1.14 (6H, t, ^3J 7.4, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.9, 196.7 (*C*2), 137.7 (*C*2'), 134.5 (*C*6'), 134.3 (*C*4'), 133.6 (*C*3'), 131.3 (*C*1'), 127.8 (*C*5'), 48.6 (*C*1), 36.1 (*C*3), 8.0 (*C*4); ESI-MS: m/z calc. for $C_{22}H_{23}O_4^+$ 351.1591 found 351.1590 [$M+H^+$].

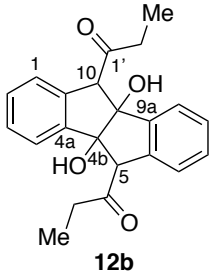
6.2.10. 1,1'-(4b,9b-Dihydroxy-4b,5,9b,10-tetrahydroindeno[2,1-*a*]indene-5,10-diyl)bis(2-phenylethan-1-one) (12a)



12a

1,2-Bis(2-(2-oxo-3-phenylpropyl)phenyl)ethane-1,2-dione (**10a**, 23.7 mg, 50.0 µmol, 1.0 eq) was dissolved in $CDCl_3$ (2.0 mL), pyrrolidine (41.1 µL, 500 µmol, 10 eq) was added and the mixture was stirred at RT for 30 min before it was washed with aq. sat. NH_4Cl (2x 2.0 mL). Each aq. layer was reextracted with CH_2Cl_2 (2.0 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the title compound **12a** as a brown oil (23.5 mg): ν_{max} (neat): 3437w, 3029w, 1704s, 1093s, 1029m, 909m, 731s, 702s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (2H, d, ^3J 7.6, C4*H*), 7.42–7.37 (4H, m), 7.35–7.29 (6H, m), 7.22 (2H, ddd, ^3J 7.6, 7.6, ^4J 1.0, C3*H*), 7.09 (2H, ddd, ^3J 7.6, 7.5, ^4J 1.2, C2*H*), 6.59 (2H, d, ^3J 7.7, C1*H*), 4.79 (2H, s, C5*H*), 4.14–4.04 (6H, m, C2'*H*, O*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 209.2 (*C*1'), 146.2 (*C*4a/*C*9a), 139.6 (*C*5a/*C*10a), 133.0, 130.3, 129.6 (*C*2), 129.0, 128.8 (*C*3), 127.6, 124.7 (*C*1), 124.3 (*C*4), 88.2 (*C*4b/*C*9b), 61.6 (*C*5/*C*10), 52.4 (*C*2'); ESI-MS: m/z calc. for $C_{32}H_{26}O_4Na^+$ 497.1723 found 497.1729 [M+Na^+]; The crude product showed a low stability silica gel.

6.2.11. 1,1'-(4b,9b-Dihydroxy-4b,5,9b,10-tetrahydroindeno[2,1-*a*]indene-5,10-diyl)bis(propan-1-one) (12b)



12b

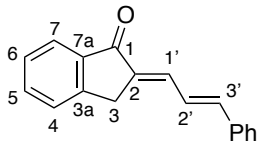
1,2-Bis(2-(2-oxobutyl)phenyl)ethane-1,2-dione (**10b**, 17.5 mg, 50.0 µmol, 1.0 eq) was dissolved in $CDCl_3$ (2.0 mL), pyrrolidine (41.1 µL, 500 µmol, 10 eq) was added and the mixture was stirred at RT for 30 min before it was washed with aq. sat. NH_4Cl (2x 2.0 mL). Each aq. layer was

reextracted with CH_2Cl_2 (2.0 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo,* to yield the title compound **12b** as a brown oil (17.5 mg): R_f 0.31 (Et_2O/*n*-pentane, 1:2); ν_{max} (neat): 3380m, 2937w, 1698s, 1458m, 1396m, 1211m, 1107s, 979m, 759s, 687m, 621m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.60 (2H, d, ^3J 7.7, C4*H*), 7.28 (2H, ddd, ^3J 7.6, 7.5, ^4J 1.2, C3*H*), 7.20 (2H, ddd, ^3J 7.5, 7.5, ^4J 1.2, C2*H*), 7.04 (2H, d, ^3J 7.6, C1*H*), 4.72 (2H, s, C5*H*/C10*H*), 4.28 (2H, s, O*H*), 2.97 (2H, dq, ^1J 18.6, ^3J 7.2, C2'*H*), 2.84 (2H, dq, ^1J 18.6, ^3J 7.1, C2'*H*), 1.14 (6H, t, ^3J 7.1, C3'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.2 (*C*1'), 146.3 (*C*4a), 139.8 (*C*5a/*C*10a), 129.7 (*C*2), 128.9 (*C*3), 124.6 (*C*1), 124.5 (*C*4), 87.8 (*C*4b/*C*9b), 63.0 (*C*5/*C*10), 38.8 (*C*2'), 7.5 (*C*3'); ESI-MS: m/z calc. for $C_{22}H_{22}O_4Na^+$ 373.1410 found 373.1413 [M+Na^+]; The crude product showed a low stability on silica gel.

6.3. General Procedure A: Preparation of Cinnamyl-indenones 19

The specified indanone **18** (1.0 eq) was dissolved in MeOH and cinnamyl aldehyde (1.1 to 1.5 eq) was added. NaOMe (0.1 eq, unless stated otherwise) was added, the mixture was sonificated until the solids dissolved and the solution was stirred at the specified temperature. After the indicated time, the precipitate was collected by filtration and the filtrate was placed in a freezer for further crystallization. The combined solids were washed with MeOH and *n*-pentane and were dried *in vacuo*.

6.3.1. (*E*)-2-((*E*)-3-Phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19a)

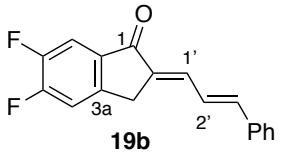


19a

Prepared according to the general procedure **A** using 1-indanone (**18a**, 66.1 g, 500 mmol, 1.0 eq), cinnamyl aldehyde (69.2 mL, 550 mmol, 1.1 eq), NaOMe (10.8 g, 50 mmol, 0.1 eq) in MeOH (1.5 L) with a reaction time of 19 h at RT to yield the title compound **19a** as a slightly yellow solid (108 g, 87%, m.p. = 116–118 °C): R_f 0.46 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3021w, 1686m, 1610s, 1463w, 1414w, 975m, 732s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82–7.79 (1H, m, C7*H*), 7.52 (1H, ddd, ^3J 7.4, 7.4, ^4J 1.2, C5*H*), 7.49–7.42 (3H, m), 7.38–7.28 (4H, m), 7.28–7.22 (1H, m), 7.02–6.92 (2H, m), 3.87 (2H, d, ^4J 1.0, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.8 (*C*1), 149.0 (*C*3a),

142.1, 139.4, 136.5, 136.3, 134.5 (*C*5), 133.5, 129.4, 129.0, 127.7, 127.4, 126.4, 124.5, 124.3 (*C*7), 30.6 (*C*3); The analytical data is in agreement with the literature.[159]

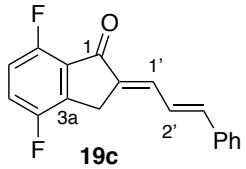
6.3.2. (*E*)-5,6-Difluoro-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19b)



19b

Prepared according to the general procedure **A** using 5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (**18b**, 2.86 g, 17.0 mmol, 1.0 eq), cinnamyl aldehyde (3.34 mL, 25.5 mmol, 1.5 eq), NaOMe (91.8 mg, 1.70 mmol, 0.1 eq) in MeOH (30 mL) with a reaction time of 72 h at 70 °C, to yield the title compound **19b** as a yellow solid (3.53 g, 74%, m.p. = 195–198 °C): R_f 0.14 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 1685m, 1587s, 1488m, 1445m, 1309s, 1209m, 1116m, 970s, 789m, 743s, 683s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.67–7.61 (1H, m, C7*H*), 7.56–7.50 (2H, m), 7.44–7.29 (5H, m, C4*H*, C1'*H*), 7.11–6.96 (2H, m, C2'*H*, C3'*H*), 3.83 (2H, s, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.6 (d, $^4J_{C\text{-}F}$ 2.5, *C*1), 154.9 (dd, $^1J_{C\text{-}F}$ 258, $^2J_{C\text{-}F}$ 14.4, *C*5), 150.9 (dd, $^1J_{C\text{-}F}$ 251, $^2J_{C\text{-}F}$ 14.0, *C*6), 145.5 (m, *C*3a), 143.1 (*C*3'), 136.3, 135.9 (m, *C*7a), 135.3, 134.2 (*C*1'), 129.6, 129.1, 127.5, 124.0 (*C*2'), 114.8 (d, $^2J_{C\text{-}F}$ 18.5, *C*4), 112.6 (dd, $^2J_{C\text{-}F}$ 17.6, $^3J_{C\text{-}F}$ 2.0, *C*7), 30.2 (*C*3); ^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled) δ = –126.0 (1F, d, $^3J_{F\text{-}F}$ 19.7), –136.8 (1F, d, $^3J_{F\text{-}F}$ 19.6); ESI-MS: m/z calc. for $C_{18}H_{13}F_2O^+$ 283.0929 found 283.0928 [$M+H^+$].

6.3.3. (*E*)-4,7-Difluoro-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19c)

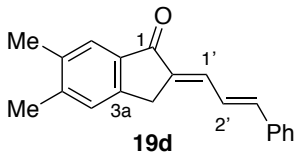


19c

Prepared according to the general procedure **A** using 4,7-difluoro-2,3-dihydro-1*H*-inden-1-one (**18c**, 5.04 g, 30.0 mmol, 1.0 eq), cinnamyl aldehyde (5.90 mL, 45.0 mmol, 1.5 eq), NaOMe (162 mg, 3.00 mmol, 0.1 eq) in MeOH (75 mL) with a reaction time of 87 h at 76 °C to yield the title compound **19c** as a yellow solid (4.79 g, 57%, m.p. = 208–211 °C): R_f 0.30 (Et_2O/*n*-pentane, 1:4);

ν_{max} (neat): 3027w, 1692s, 1485s, 1335m, 1239s, 991m, 806m, 746s, 687s; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.44 (2H, m), 7.40–7.24 (4H, m, C5*H*), 7.21–7.14 (1H, m, C1'*H*), 7.06–6.90 (3H, m), 3.79 (2H, s, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 189.3 (*C*1), 155.7 (dd, $^{1}J_{C\text{-}F}$ 245, $^{4}J_{C\text{-}F}$ 2.6, *C*4), 155.5 (dd, $^{1}J_{C\text{-}F}$ 259, $^{4}J_{C\text{-}F}$ 2.7, *C*7), 143.5, 136.2, 135.0, 134.3, 129.7, 129.1, 128.7, 127.6, 123.9, 122.0 (dd, $^{2}J_{C\text{-}F}$ 22.8, $^{3}J_{C\text{-}F}$ 8.1, *C*5), 116.2 (dd, $^{2}J_{C\text{-}F}$ 22.7, $^{3}J_{C\text{-}F}$ 6.4, *C*6), 26.8 (*C*3); ^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) δ = –120.4 (1F, d, $^{5}J_{F\text{-}F}$ 24.3), –124.6 (1F, d, $^{5}J_{F\text{-}F}$ 22.9); ESI-MS: m/z calc. for $C_{18}H_{13}F_2O^+$ 283.0929 found 283.0927 [M+H$^+$].

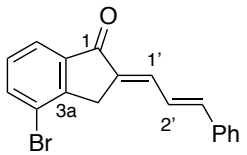
6.3.4. (*E*)-5,6-Dimethyl-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19d)



19d

Prepared according to the general procedure **A** using 5,6-dimethyl-2,3-dihydro-1*H*-inden-1-one (**18d**, 1.40 g, 8.75 mmol, 1.0 eq), cinnamyl aldehyde (1.65 mL, 13.1 mmol, 1.5 eq), NaOMe (47.3 mg, 875 µmol, 0.1 eq) in MeOH (30 mL) with a reaction time of 16 h at RT to yield the title compound **19d** as a slightly yellow solid (1.92 g, 80%, m.p. = 182–185 °C): R_f 0.32 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3027w, 1686s, 1620s, 1451w, 1361w, 1319m, 1169w, 1127m, 973w, 928w, 691w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (1H, s), 7.54–7.50 (2H, m), 7.41–7.35 (3H, m), 7.34–7.27 (2H, m), 7.07–6.98 (2H, m), 3.77 (2H, s), 2.37 (3H, s), 2.32 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.7, 147.2, 144.8, 141.5, 137.6, 137.1, 136.6, 136.6, 132.8, 129.2, 129.0, 127.4, 127.1, 124.8, 124.7, 30.1, 21.0, 19.9; ESI-MS: m/z calc. for $C_{20}H_{19}O^+$ 275.1430 found 275.1427 [M+H$^+$].

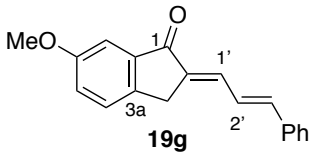
6.3.5. (*E*)-4-Bromo-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one



Prepared according to the general procedure **A** using 4-bromo-2,3-dihydro-1*H*-inden-1-one (6.33 g, 30.0 mmol, 1.0 eq), cinnamyl aldehyde (4.53 mL, 36.0 mmol, 1.2 eq), NaOMe (162 mg, 3.00 mmol, 0.1 eq) in MeOH (100 mL) with a reaction time of 16 h at RT to yield the title compound

as a yellow solid (7.75 g, 79%, m.p. = 166–169 °C): R_f 0.50 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3055w, 3028w, 1695s, 1592s, 1452m, 1323m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.75 (1H, d, ^3J 7.5, C7*H*), 7.69 (1H, dd, ^3J 7.8, ^4J 0.9, C5*H*), 7.51–7.46 (2H, m), 7.41–7.36 (1H, m, C1'*H*), 7.35–7.30 (2H, m), 7.30–7.22 (2H, m), 7.06–6.97 (2H, m, C2'*H*, C3'*H*), 3.71 (2H, d, ^4J 1.5, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.0 (*C*1), 149.0 (*C*3a), 143.1 (*C*3'), 141.4, 137.2 (*C*5'), 136.3, 135.2, 134.6 (*C*1'), 129.6, 129.5, 129.0, 127.6, 124.2 (*C*2'), 123.1 (*C*7), 121.9, 31.9 (*C*3); ESI-MS: m/z calc. for $C_{18}H_{14}BrO^+$ 325.0223 found 325.0220 [M+H$^+$].

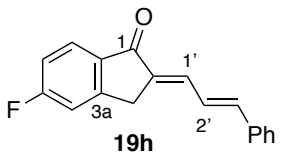
6.3.6. (*E*)-6-Methoxy-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19g)



19g

Prepared according to the general procedure **A** using 6-methoxy-2,3-dihydro-1*H*-inden-1-one (**18g**, 4.86 g, 30.0 mmol, 1.0 eq), cinnamyl aldehyde (5.90 mL, 45.0 mmol, 1.5 eq), NaOMe (162 mg, 3.00 mmol, 0.1 eq) in MeOH (170 mL) with a reaction time of 44 h at RT to yield the title compound **19g** as a slightly yellow solid (7.02 g, 85%, m.p. = 145–147 °C): R_f 0.26 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3027w, 1686m, 1614s, 1490s, 1283s, 1165w, 1112w, 1027w, 972w, 751w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55–7.50 (2H, m), 7.43–7.36 (4H, m), 7.35–7.30 (2H, m), 7.19 (1H, dd, ^3J 8.3, ^4J 2.6, C5*H*), 7.05–7.00 (2H, m), 3.85 (3H, s, OCH_3), 3.78 (2H, d, ^4J 1.6, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.7 (*C*1), 159.7 (*C*6), 142.0, 141.8, 140.6, 137.1, 136.5, 133.3, 129.3, 129.0, 127.4, 127.1, 124.5, 123.8 (*C*5), 105.7, 55.8 (O*C*H$_3$), 29.8 (*C*3); ESI-MS: m/z calc. for $C_{19}H_{17}O_2^+$ 277.1223 found 277.1222 [M+H$^+$].

6.3.7. (*E*)-5-Fluoro-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19h)

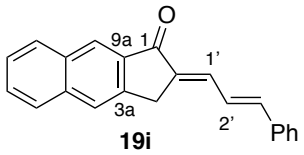


19h

Prepared according to the general procedure **A** using 5-fluoro-2,3-dihydro-1*H*-inden-1-one (**18h**, 9.76 g, 65.0 mmol, 1.0 eq), cinnamyl aldehyde (9.00 mL, 71.5 mmol, 1.1 eq), NaOMe (442 mg,

6.50 mmol, 0.1 eq) in MeOH (250 mL) with a reaction time of 65 h at RT to yield the title compound **19h** as a slightly yellow solid (14.9 g, 87%, m.p. = 168–171 °C): R_f 0.43 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 2931w, 1692s, 1615s, 1478m, 1415m, 1331m, 1238s, 1081s, 940s, 862m, 741s, 678s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.87 (1H, dd, ^3J 8.4, $^4J_{H\text{-}F}$ 5.4, C7*H*), 7.52 (2H, m), 7.42–7.30 (4H, m, C1'*H*), 7.19 (1H, d, $^3J_{H\text{-}F}$ 8.2, C4*H*), 7.10 (1H, ddd, ^3J 8.8 , 8.7, ^4J 1.6, C6*H*), 7.08–6.97 (2H, m, C2'*H*, C3'*H*), 3.85 (2H, s, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 192.0 (*C*1), 167.0 (d, $^1J_{C\text{-}F}$ 254, *C*5), 151.8 (d, $^3J_{C\text{-}F}$ 10.7, *C*3a), 142.4 (*C*2'), 136.4, 135.8 (*C*8), 135.8, 133.5 (*C*1'), 129.4, 129.0, 127.5, 126.6 (d, $^3J_{C\text{-}F}$ 10.8), 124.2 (*C*3'), 115.9 (d, $^2J_{C\text{-}F}$ 24.0, *C*6), 113.1 (d, $^2J_{C\text{-}F}$ 22.7, *C*4), 30.6 (d, $^4J_{C\text{-}F}$ 1.8, *C*3); ESI-MS: m/z calc. for $C_{18}H_{14}FO^+$ 265.1023 found 265.1021 [M+H$^+$]. ^{19}F NMR (471 MHz, $CDCl_3$, proton decoupled) δ = 102.9 (1F, s); ESI-MS: m/z calc. for $C_{18}H_{14}FO^+$ 265.1023 found 265.1021 [M+H$^+$].

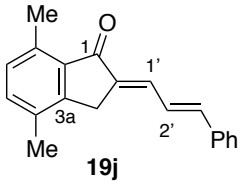
6.3.8. (*E*)-2-((*E*)-3-Phenylallylidene)-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (19i)



19i

Prepared according to the general procedure **A** using 2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (**18i**, 3.64 g, 20.0 mmol, 1.0 eq), cinnamyl aldehyde (3.78 mL, 30.0 mmol, 1.5 eq), NaOMe (136 mg, 2.00 mmol, 0.1 eq) in MeOH (600 mL) with a reaction time of 18 h at RT to yield the title compound **19i** as a brown solid (4.23 g, 71%, m.p. = 194 °C (decomp.)): R_f 0.34 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3032w, 1688s, 1609s, 1279m, 1172m, 1123m, 974m, 944m, 878m, 849w, 778m, 747s, 693s, 622m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.44 (1H, s, C9*H*), 8.00 (1H, d, *J* 8.3, C8*H*), 7.93 (1H, s, C4*H*), 7.88 (1H, d, *J* 8.2, C5*H*), 7.60–7.53 (3H, m), 7.53–7.47 (2H, m), 7.42–7.37 (2H, m), 7.36–7.32 (1H, m), 7.11–7.06 (2H, m), 4.04 (2H, s, C3*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 194.1 (*C*1), 142.5 (*C*3a), 142.4, 137.4 (*C*4a), 137.1 (*C*9a), 137.0, 136.5, 133.8, 132.7 (*C*8a), 130.5 (*C*8), 129.4, 129.0, 128.6 (*C*6), 128.0 (*C*5), 127.5, 126.3 (*C*7), 125.0 (*C*9), 124.6 (*C*4), 124.6, 30.3 (*C*3); ESI-MS: m/z calc. for $C_{22}H_{17}O^+$ 297.1274 found 297.1273 [M+H$^+$].

6.3.9. (*E*)-4,7-Dimethyl-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (19j)

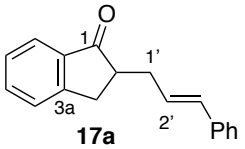


19j

Prepared according to the general procedure **A** using 4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (**18j**, 4.81 g, 30.0 mmol, 1.0 eq), cinnamyl aldehyde (5.66 mL, 45.0 mmol, 1.5 eq), NaOMe (162 mg, 3.00 mmol, 0.1 eq) in MeOH (70 mL) with a reaction time of 17 h at RT to yield the title compound **19j** as a slightly yellow solid (6.49 g, 79%, m.p. = 156–160 °C): R_f 0.19 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3032w, 2914w, 1682s, 1615s, 1497m, 1326m, 1272m, 1247s, 1155m, 1118m, 987s, 956m, 813m, 742s, 682s; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57–7.50 (2H, m, C6*H*), 7.41–7.29 (4H, m), 7.26 (1H, d, *J* 7.5, C5*H*), 7.13–6.98 (3H, m), 3.68 (2H, s, C3*H*), 2.69 (3H, s, CH_3), 2.36 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 195.2 (*C*1), 148.6 (*C*3a), 141.4, 136.9, 136.6, 136.6, 136.5, 134.5 (*C*5), 132.4, 132.3 (*C*4), 129.7, 129.2, 129.0, 127.4 (*C*6), 124.7, 29.2 (*C*3), 18.3 (*C*H_3), 17.8 (*C*H_3); ESI-MS: m/z calc. for $C_{20}H_{19}O^+$ 275.1430 found 275.1425 [$M+H^+$].

6.4. Procedures B: 1,4-Reduction of Dienones[106]

6.4.1. 2-Cinnamyl-2,3-dihydro-1*H*-inden-1-one (17a)

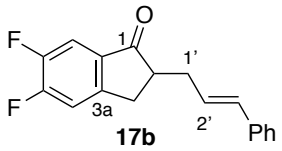


17a

(*E*)-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19a**, 73.9 g, 300 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (1.5 L) and cooled to –30 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (114 g, 450 mmol, 1.5 eq) was added followed by the dropwise addition of $TiCl_4$ (1.00 molL^{-1} in CH_2Cl_2, 360 mL, 360 mmol, 1.2 eq) over 1.5 h. The black mixture was warmed up to –10 °C over 2 h before aq. sat. NH_4Cl (400 mL) and H_2O (600 mL) were added carefully. The org. layer was separated and washed with H_2O (1.0 L). The aq. layer was reextracted with CH_2Cl_2 (2x 500 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:2 to 1:1) to

yield the title compound **17a** as a slightly yellow oil (33.9 g, 46%); R_f 0.30 (CH_2Cl_2/petrol ether, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77 (1H, d, ^3J 7.7, C7*H*), 7.58 (1H, ddd, ^3J 7.5, 7.5, ^4J 1.2, C5*H*), 7.46–7.42 (1H, m, C4*H*), 7.39–7.35 (1H, m, C6*H*), 7.33–7.26 (4H, m), 7.22–7.18 (1H, m), 6.48 (1H, d, ^3J 15.7, C3'*H*), 6.24–6.17 (1H, m, C2'*H*), 3.31 (1H, dd, ^2J 17.2, ^3J 7.7, C3*H*), 2.94–2.82 (3H, m, C2*H*, C3*H*, C1'*H*), 2.48–2.38 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.2 (*C*1), 153.9 (*C*3a), 137.4, 136.8 (*C*7a), 135.0 (*C*5), 132.3 (*C*3'), 128.7, 127.6 (*C*6), 127.4 (*C*2'), 127.4, 126.8 (*C*4), 126.2, 124.1 (*C*7), 47.2 (*C*2), 34.9 (*C*1'), 32.2 (*C*3).

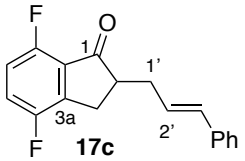
6.4.2. 2-Cinnamyl-5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (17b)



17b

(*E*)-5,6-difluoro-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19b**, 2.26 g, 8.00 mmol, 1.0 eq) was dissolved in toluene (250 mL) and cooled to –40 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3.04 g, 12.0 mmol, 1.5 eq) was added followed by the dropwise addition of $TiCl_4$ (1.00 molL^{-1} in CH_2Cl_2, 9.60 mL, 9.60 mmol, 1.2 eq). The black mixture was stirred at –40 °C for 30 min before it was warmed up to RT over 1 h. Aq. HCl (1.00 molL^{-1}, 100 mL) was added and the org. layer was separated. The aq. layer was reextracted with EtOAc (2x 50 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 2:1) to yield the title compound **17b** as a white solid (2.08 g, 91%, m.p. = 109–112 °C): R_f 0.58 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3044w, 1705s, 1598w, 1494s, 1441m, 1320s, 1266m, 1216m, 1104m, 970m, 910m, 748m, 693m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.56–7.50 (1H, m, C7*H*), 7.33–7.18 (6H, m), 6.47 (1H, d, ^3J 15.7, C3'*H*), 6.15 (1H, dt, ^3J 15.7, ^4J 7.1, C2'*H*), 3.30–3.22 (1H, m, C3*H*), 2.99–2.80 (3H, m, C1'*H*, C2*H*, C3*H*), 2.48–2.40 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 205.8 (d, $^5J_{C\text{-}F}$ 2.9, *C*1), 155.5 (dd, $^1J_{C\text{-}F}$ 260, $^2J_{C\text{-}F}$ 14.3), 151.2 (dd, $^1J_{C\text{-}F}$ 252, $^2J_{C\text{-}F}$ 14.5), 150.4 (dd, $^3J_{C\text{-}F}$ 8.0, $^4J_{C\text{-}F}$ 2.4), 137.2, 133.1 (dd, $^3J_{C\text{-}F}$ 5.1, $^4J_{C\text{-}F}$ 2.3), 132.8 (*C*3'), 128.7, 127.5, 126.6 (*C*2'), 126.3, 115.0 (d, $^2J_{C\text{-}F}$ 18.0), 112.1 (dd, $^2J_{C\text{-}F}$ 17.4, $^3J_{C\text{-}F}$ 2.3, *C*7), 47.6 (*C*2), 34.8 (*C*1'), 31.8 (*C*3); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –125.2 (1F, m), –136.8 (1F, m); ESI-MS: m/z calc. for $C_{18}H_{15}F_2O^+$ 285.1085 found 285.1084 [M+H$^+$].

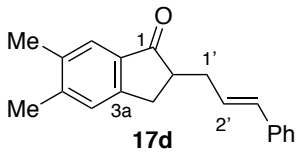
6.4.3. 2-Cinnamyl-4,7-difluoro-2,3-dihydro-1*H*-inden-1-one (17c)



17c

(*E*)-4,7-Difluoro-2-((*E*)-3-phenyl-allylidene)-2,3-dihydro-1*H*-inden-1-one (**19c**, 2.82 g, 10.0 mmol, 1.0 eq) was dissolved in THF (50 mL) and cooled to 0 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3.80 g, 15.0 mmol, 1.5 eq) was added followed by the dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 12.0 mL, 12.0 mmol, 1.2 eq). The black mixture was stirred at 0 °C for 2 h before aq. HCl (1.00 $molL^{-1}$, 50 mL) was added and the org. layer was separated. The aq. layer was extracted with Et_2O (2x 70 mL) and the combined org. layers were washed with an aq. HCl (1.00 $molL^{-1}$, 2x 70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:1) to yield the title compound **17c** as a slightly yellow oil (1.91 g, 67%): R_f 0.49 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 1720s, 1626m, 1489s, 1243m, 969w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28–7.19 (4H, m), 7.17–7.11 (2H, m), 6.89 (1H, ddd, ^3J 8.4, $^3J_{H\text{-}F}$ 8.6, $^4J_{H\text{-}F}$ 3.3, C6*H*), 6.42 (1H, d, ^3J 15.8, C3'*H*), 6.10 (1H, dt, ^3J 15.7, 7.3, C2'*H*), 3.24 (1H, dd, ^2J 18.6, ^3J 8.9, C3*H*), 2.88–2.73 (3H, m, C2*H*, C3*H*, C1'*H*), 2.45–2.35 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.1 (*C*1), 155.8 (dd, $^1J_{C\text{-}F}$ 246, $^4J_{C\text{-}F}$ 2.3, *C*4), 154.9 (dd, $^1J_{C\text{-}F}$ 260, $^4J_{C\text{-}F}$ 2.8, *C*7), 140.7 (dd, $^2J_{C\text{-}F}$ 22.1, $^4J_{C\text{-}F}$ 2.9, *C*3a), 137.1, 133.0 (*C*3'), 128.7, 127.5, 126.3, 126.3 (*C*2'), 126.0 (dd, $^2J_{C\text{-}F}$ 15.4, $^3J_{C\text{-}F}$ 4.8, *C*7a), 122.5 (dd, $^2J_{C\text{-}F}$ 22.3, $^3J_{C\text{-}F}$ 8.6, *C*5), 116.0 (dd, $^2J_{C\text{-}F}$ 22.5, $^3J_{C\text{-}F}$ 6.7, *C*6), 47.5 (*C*2), 34.7 (*C*1'), 27.9 (*C*3); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –119.9 (1F, ddd, $^3J_{F\text{-}H}$ 23.9, $^4J_{F\text{-}H}$ 8.3, $^5J_{F\text{-}F}$ 3.6), –124.2 (1F, ddd, $^3J_{F\text{-}H}$ 23.7, $^4J_{F\text{-}H}$ 7.7, $^5J_{F\text{-}F}$ 3.1); ESI-MS: m/z calc. for $C_{18}H_{15}F_2O^+$ 285.1085 found 285.1081 [$M+H^+$].

6.4.4. 2-Cinnamyl-5,6-dimethyl-2,3-dihydro-1*H*-inden-1-one (17d)

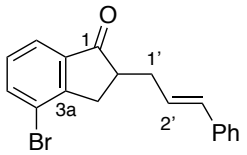


17d

(*E*)-5,6-Dimethyl-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19d**, 1.01 g, 4.00 mmol, 1.0 eq) was suspended in THF (60 mL) and cooled to 0 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.52 g, 6.00 mmol, 1.5 eq) was added, followed by dropwise

addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 4.80 mL, 4.80 mmol, 1.2 eq). The black mixture was stirred at 0 °C for 2 h before aq. HCl (1.00 $molL^{-1}$, 30 mL) and Et_2O (50 mL) were added. The org. layer was separated and the aq. layer was extracted with Et_2O (2x 75 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 2:1) to yield the title compound **17d** as a yellow oil along with an inseparable regioisomer (669 mg, 61%): R_f 0.36 (CH_2Cl_2/*n*-pentane, 2:1); ν_{max} (neat): 3025w, 2921w, 1704s, 1617m, 1452w, 1321w, 1258w, 1168w, 1102w, 967w, 745w, 695w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52 (1H, s), 7.33–7.23 (4H, m), 7.22–7.16 (2H, m), 6.46 (1H, d, *J* 15.9), 6.19 (1H, dt, *J* 15.7, 7.2), 3.25–3.17 (1H, m), 2.87–2.77 (3H, m), 2.43–2.35 (1H, m), 2.32 (3H, s), 2.29 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.9, 152.0, 145.2, 137.4, 136.4, 134.9, 132.1, 128.6, 127.6, 127.5, 127.3, 126.2, 124.4, 47.4, 35.0, 31.7, 20.8, 19.8; ESI-MS: m/z calc. for $C_{20}H_{20}ONa^+$ 299.1406 found 299.1409 [M+Na^+].

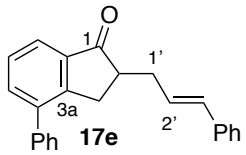
6.4.5. 4-Bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one



(*E*)-4-Bromo-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (1.95 g, 6.00 mmol, 1.0 eq) was dissolved in THF (100 mL) and cooled to 0 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2.28 g, 9.00 mmol, 1.5 eq) was added followed by dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 7.20 mL, 7.20 mmol, 1.2 eq). The black mixture was stirred at 0 °C for 45 min before aq. HCl (1.00 $molL^{-1}$, 80 mL) was added. Et_2O (40 mL) was added and the org. layer was separated. The aq. layer was extracted with Et_2O (3x 100 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 2:1) to yield the title compound as a yellow oil (1.50 g, 77%): R_f 0.63 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3026w, 2912w, 1712s, 1454m, 1423m, 1326m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.69 (1H, dd, ^3J 7.7, ^4J 1.0, C5*H*), 7.65 (1H, d, ^3J 7.6, C7*H*), 7.29–7.25 (2H, m), 7.25–7.19 (3H, m), 7.17–7.12 (1H, m), 6.44 (1H, d, ^3J 15.7, C3'*H*), 6.14 (1H, dt, ^3J 15.7, 6.7, C2'*H*), 3.20 (1H, dd, ^2J 17.5, ^3J 7.4, C3*H*), 2.86–2.74 (3H, m, C2*H*, C3*H*, C1'*H*), 2.42–2.33 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.3 (*C*1), 153.5, 138.8, 137.7 (*C*5), 137.3, 132.7

(*C*3'), 129.4, 128.7, 127.5, 126.8 (*C*2'), 126.3, 122.9 (*C*7), 122.4, 47.3 (*C*2), 34.8 (*C*1'), 33.4 (*C*3); ESI-MS: m/z calc. for $C_{18}H_{16}BrO^+$ 327.0379 found 327.0376 [$M+H^+$].

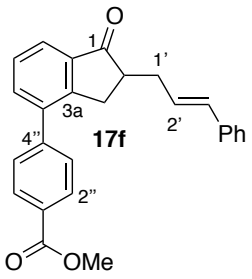
6.4.6. 2-Cinnamyl-4-phenyl-2,3-dihydro-1*H*-inden-1-one (17e)



17e

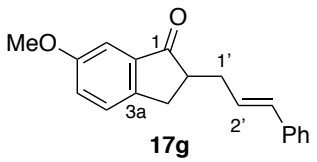
4-Bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (1.31 g, 4.00 mmol, 1.0 eq), phenylboronic acid (585 mg, 4.80 mmol, 1.2 eq) and Cs_2CO_3 (1.96 g, 6.00 mmol, 1.5 eq) were suspended in THF (27 mL) and H_2O (3.0 mL). The suspension was degassed for 10 min before $Pd(PPh_3)_4$ (231 mg, 200 µmol, 5.0 mol%) was added and the mixture was heated to 80 °C for 14 h. H2O (20 mL) and Et_2O (20 mL) were added and the org. layer was separated and the aq. layer was extracted with Et_2O (2x 50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 2:1) to yield the title compound **17e** as a slightly yellow oil (1.20 g, 93%): R_f 0.55 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3025w, 1706s, 1596w, 1427w, 1329w, 1254m, 1205w, 1080m, 970m, 910m, 740s, 696s, 611m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77 (1H, dd, ^3J 7.6, ^4J 1.1, C7*H*), 7.57 (1H, dd, ^3J 7.5, ^4J 1.2, C5*H*), 7.46–7.40 (5H, m), 7.39–7.34 (1H, m), 7.30–7.22 (4H, m), 7.19–7.14 (1H, m), 6.44 (1H, d, ^3J 15.8, C2'*H*), 6.18 (1H, dt, ^3J 15.7, 7.0, C2'*H*), 3.33 (1H, dd, ^2J 17.3, ^3J 7.8, C3*H*), 2.94–2.79 (3H, m, C2*H*, C3*H*, C1'*H*), 2.46–2.37 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.0 (*C*1), 151.2 (*C*3a), 140.4, 139.2, 137.3, 137.2, 135.1, 132.2 (*C*3'), 128.7, 128.6, 128.1, 127.8, 127.3 (*C*2'), 126.2, 123.0 (*C*7), 47.5 (*C*2), 34.7 (*C*1'), 32.1 (*C*3); ESI-MS: m/z calc. for $C_{24}H_{21}O^+$ 325.1587 found 325.1585 [$M+H^+$].

6.4.7. Methyl 4-(2-cinnamyl-1-oxo-2,3-dihydro-1*H*-inden-4-yl)benzoate (17f)



A microwave tube was charged with 4-bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (327 mg, 1.00 mmol, 1.0 eq), (4-(methoxycarbonyl)phenyl)boronic acid (216 mg, 1.20 mmol, 1.2 eq), cesium carbonate (489 mg, 1.5 mmol, 1.5 eq) and $Pd(PPh_3)_4$ (57.8 mg, 50.0 µmol, 5.0 mol%). THF (10 mL) added and the mixture was heated to 80 °C for 6 h before the mixture was cooled to RT and diluted with Et_2O (30 mL). The mixture was washed with H_2O (30 mL), the aq. layer was extracted with Et_2O (2x 50 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to yield the title compound **17f** as a slightly yellow oil (358 mg, 94%): R_f 0.41 (CH_2Cl_2); ν_{max} (neat): 3026w, 2925w, 1714s, 1608w, 1435w, 1279s, 1184w, 1112m, 1018w, 967w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (2H, d, ^2J 8.5, C2''*H*/C6''*H*), 7.82 (1H, dd, ^3J 7.5, ^4J 0.8, C7*H*), 7.61 (1H, dd, ^3J 7.5, ^4J 1.0, C5*H*), 7.53–7.47 (3H, m, C6*H*, C3''*H*, C5''*H*), 7.31–7.24 (4H, m), 7.22–7.16 (1H, m), 6.46 (1H, d, ^3J 15.7, C3'*H*), 6.18 (1H, dt, ^3J 15.8, 7.0, C2'*H*), 3.94 (3H, s, CO_2CH_3) 3.37–3.29 (1H, m, C3*H*), 2.94–2.82 (3H, m, C2*H*, C3*H*, C1'*H*), 2.50–2.40 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.8 (*C*1), 166.9 (CO_2CH_3), 151.1 (*C*3a), 142.8 (*C*4''), 139.5, 137.4, 137.2, 135.0 (*C*5), 132.4 (*C*3'), 130.1 (*C*2'', *C*6''), 129.6, 128.7, 128.6, 128.3, 127.4, 127.1 (*C*2'), 126.2, 123.8 (*C*7), 52.4 (CO_2CH_3), 47.5 (*C*2), 34.7 (*C*1'), 32.1 (*C*3); ESI-MS: m/z calc. for $C_{26}H_{22}O_3Na^+$ 405.1461 found 405.1464 [$M+Na^+$].

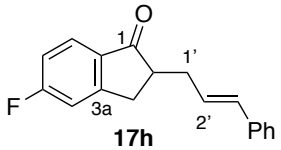
6.4.8. 2-Cinnamyl-6-methoxy-2,3-dihydro-1*H*-inden-1-one (17g)



(*E*)-6-Methoxy-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19g**, 2.21 g, 8.00 mmol, 1.0 eq) was dissolved in THF (80 mL) and cooled to –30 °C. Diethyl 2,6-dimethyl-1,4-

dihydropyridine-3,5-dicarboxylate (3.04 g, 12.0 mmol, 1.5 eq) was added followed by dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 9.60 mL, 9.60 mmol, 1.2 eq). The black mixture was stirred at –30 °C for 1.5 h before aq. HCl (1.00 $molL^{-1}$, 50 mL) was added. H_2O (50 mL) and Et_2O (50 mL) were added and the org. layer was separated. The aq. layer was extracted with Et_2O (2x 50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:1 to 2:1) to yield the title compound **17g** as a slightly yellow solid (1.07 g, 48%, m.p. = 100–101 °C): R_f 0.24 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 2924w, 1702s, 1615w, 1490s, 1433m, 1276s, 1232m, 1164m, 1026m, 966m, 828w, 744m, 694m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34–7.26 (5H, m), 7.23–7.17 (3H, m), 6.48 (1H, d, ^3J 15.6, C3'*H*), 6.20 (1H, dt, ^3J 15.7, 6.7, C2'*H*), 3.84 (3H, s, OCH_3), 3.27–3.20 (1H, m, C3*H*), 2.90–2.81 (3H, m, C2*H*, C3*H*, C1'*H*), 2.48–2.38 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.2 (*C*1), 159.6 (*C*6), 146.7, 137.9, 137.4, 132.3 (*C*3'), 128.7, 127.4, 127.4 (*C*2'), 126.2, 124.4, 105.2, 55.7 (O*C*H_3), 48.0 (*C*2), 35.0 (*C*1'), 31.5 (*C*3); ESI-MS: m/z calc. for $C_{19}H_{19}O_2^+$ 279.1380 found 279.1376 [M+H^+].

6.4.9. 2-Cinnamyl-5-fluoro-2,3-dihydro-1*H*-inden-1-one (17h)

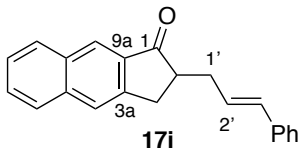


17h

(*E*)-5-Fluoro-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19h**, 1.59 g, 6.00 mmol, 1.0 eq) was dissolved in toluene (150 mL) and cooled to –40 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2.28 g, 9.00 mmol, 1.5 eq) was added, followed by dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 7.20 mL, 7.20 mmol, 1.2 eq). The black mixture was stirred at –40 °C for 30 min before it was warmed up to RT over 1 h. Aq. HCl (1.00 $molL^{-1}$, 100 mL) was added and the org. layer was separated. The aq. layer was extracted with EtOAc (2x 100 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:1) to yield the title compound **17h** as a yellow oil (660 mg, 41%): R_f 0.55 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3026w, 2914w, 1708s, 1592m, 1482m, 1432m, 1332m, 1245s, 1084m, 966m, 857m, 744m, 693m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.76 (1H, dd, ^3J 8.2, $^4J_{H\text{-}F}$ 5.3, C7*H*), 7.33–7.24 (4H, m), 7.22–7.17 (1H, m), 7.10–7.02 (2H, m), 6.47 (1H, d, ^3J 15.7, C3'*H*), 6.17 (1H, dt, ^3J 15.7, 6.9, C2'*H*), 3.32–3.22 (1H, m, C3*H*), 2.93–2.80 (3H, m, C2*H*, C3*H*, C1'*H*), 2.47–2.37 (1H, m, C1'*H*); ^{13}C NMR

(126 MHz, $CDCl_3$) δ = 206.1 (*C*1), 167.4 (d, $^1J_{C\text{-}F}$ 256, *C*5), 156.7 (d, $^3J_{C\text{-}F}$ 10.1, *C*3a), 137.2, 133.1 (d, $^4J_{C\text{-}F}$ 1.7), 132.5 (*C*3'), 128.6, 127.4, 127.0 (*C*2'), 126.3 (d, $^3J_{C\text{-}F}$ 10.4, *C*7), 126.2, 115.8 (d, $^2J_{C\text{-}F}$ 23.8), 113.3 (d, $^2J_{C\text{-}F}$ 22.2), 47.4 (*C*2), 34.8 (*C*1'), 32.1 (*C*3); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –102.7 (1F, m); ESI-MS: m/z calc. for $C_{18}H_{16}FO^+$ 267.1180 found 267.1176 [$M+H^+$].

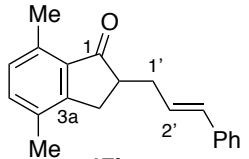
6.4.10. 2-Cinnamyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (17i)



17i

(*E*)-2-((*E*)-3-Phenylallylidene)-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (**19i**, 1.19 g, 4.00 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (120 mL) and cooled to –30 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.52 g, 6.00 mmol, 1.5 eq) was added, followed by the dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 4.80 mL, 4.80 mmol, 1.2 eq). The black mixture was warmed up to RT over 4 h. Aq. sat. NH_4Cl (100 mL) was added and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 50 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 2:1) to yield the title compound **17i** as a slightly yellow oil (859 mg, 72%): R_f 0.18 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3026w, 2923w, 1703s, 1626m, 1495m, 1448m, 1386m, 1326m, 1277m, 1226w, 1165m, 1095m, 969s, 894m, 739s, 694s, 623m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (1H, s, C9*H*), 7.97 (1H, dd, *J* 8.3, 0.6, C8*H*), 7.85–7.82 (2H, m), 7.57 (1H, ddd, *J* 6.8, 6.8, 1.2, C6*H*), 7.48 (1H, ddd, *J* 6.8, 6.8, 1.2, C7*H*), 7.34–7.30 (2H, m), 7.30–7.25 (2H, m), 7.21–7.17 (1H, m), 6.50 (1H, d, *J* 15.9, C3'*H*), 6.23 (1H, dt, *J* 15.7, 6.9, C2'*H*), 3.48 (1H, dd, *J* 16.9, 8.5, C3*H*), 3.08 (1H, ddd, *J* 16.9, 4.7, 1.3, C3*H*), 2.99–2.88 (2H, m, C1*H*, C1'*H*), 2.53–2.44 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.4 (*C*1), 146.5 (*C*3a), 137.5 (*C*4a), 137.4, 134.5 (*C*9a), 132.5 (*C*8a), 132.4 (*C*3'), 130.5, 128.7 (*C*6), 128.6, 127.9 (*C*5), 127.4 (*C*2'), 126.2 (*C*7), 124.9, 124.8 (*C*9), 50.0 (*C*3), 35.1 (*C*1'), 31.8 (*C*2); ESI-MS: m/z calc. for $C_{22}H_{18}ONa^+$ 321.1250 found 321.1249 [$M+Na^+$].

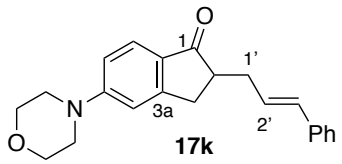
6.4.11. 2-Cinnamyl-4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (17j)



17j

(*E*)-4,7-Dimethyl-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one (**19j**, 1.10 g, 4.00 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (60 mL) and cooled to –30 °C. Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1.52 g, 6.00 mmol, 1.5 eq) was added, followed by the dropwise addition of $TiCl_4$ (1.00 $molL^{-1}$ in CH_2Cl_2, 4.80 mL, 4.80 mmol, 1.2 eq). The black mixture was stirred at –30 °C for 1 h before warming to RT. H_2O (25 mL) and aq. sat. NH_4Cl (25 mL) were added and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 50 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:1) to yield the title compound **17j** as a slightly yellow oil (597 mg, 54%): R_f 0.33 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3025w, 2921w, 1701s, 1586w, 1496w, 1440w, 1331w, 1249w, 1087w, 967w, 822w, 745w, 694w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36–7.33 (2H, m), 7.31–7.27 (2H, m), 7.24 (1H, d, *J* 7.5), 7.22–7.18 (1H, m), 7.02 (1H, d, *J* 7.5), 6.49 (1H, d, *J* 15.7), 6.24 (1H, dt, *J* 15.7, 6.7), 3.14 (1H, dd, *J* 17.2, 7.9), 2.92–2.85 (1H, m), 2.82–2.76 (1H, m), 2.70 (1H, dd, *J* 17.3, 4.1), 2.61 (3H, s), 2.42–2.34 (1H, m), 2.28 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 209.3, 153.3, 137.5, 136.2, 134.7, 133.9, 132.8, 132.0, 129.4, 128.6, 127.9, 127.3, 126.2, 47.3, 35.1, 30.8, 18.1, 17.6; ESI-MS: m/z calc. for $C_{20}H_{21}O^+$ 277.1587 found 277.1584 [M+H^+].

6.4.12. 2-Cinnamyl-5-morpholino-2,3-dihydro-1*H*-inden-1-one (17k)

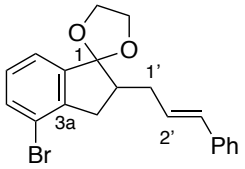


17k

2-Cinnamyl-5-fluoro-2,3-dihydro-1*H*-inden-1-one (**17h**, 666 mg, 2.50 mmol, 1.0 eq) was dissolved in DMSO (25 mL) and morpholine (4.36 mL, 50.0 mmol, 20 eq) was added and heated to 110 °C for 20 h. The mixture was cooled to RT and diluted with Et_2O (50 mL) and washed with H_2O (75 mL). The aq. layer was extracted with Et_2O (100 mL) and the combined org. layers were washed with H_2O (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was

recrystallized from Et_2O (20 mL). The yellow solid was filtered off (460.5 mg, 55%) and the filtrate was concentrated *in vacuo* and purified by column chromatography (Et_2O) yielding additional product **17k** (172.2 mg, 21%): R_f 0.70 (Et_2O); ν_{max} (neat): 2845w, 2341w, 1682s, 1596s, 1500w, 1449w, 1367m, 1245s, 1103m, 1040m, 955m, 879m, 741m, 694m, 616m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66 (1H, d, ^3J 8.7, C7*H*), 7.35–7.24 (4H, m), 7.23–7.17 (1H, m), 6.87 (1H, dd, ^3J 8.7, ^4J 2.2, C6*H*), 6.77 (1H, d, ^4J 1.7, C4*H*), 6.46 (1H, d, ^3J 15.7, C3'*H*), 6.20 (1H, dt, ^3J 15.7, 7.2, C2'*H*), 3.89–3.82 (4H, m, NC*H*$_2$CH$_2$O), 3.36–3.30 (4H, m, NCH$_2$C*H*$_2$O), 3.24–3.16 (1H, m, C3*H*), 2.89–2.78 (3H, m, C2*H*, C3*H*, C1'*H*), 2.45–2.35 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 206.0 (*C*1), 156.5 (*C*3a), 156.2 (*C*5), 137.5, 132.1 (*C*3'), 128.6, 128.0 (*C*7a), 127.8 (*C*2'), 127.3, 126.2, 125.5 (*C*7), 114.4 (*C*6), 109.9 (*C*4), 66.7 (N*C*H$_2$CH$_2$O), 47.9 (NCH$_2$*C*H$_2$O), 47.3 (*C*2), 35.3 (*C*1'), 32.3 (*C*3); ESI-MS: m/z calc. for $C_{22}H_{24}NO_2^+$ 334.1802 found 334.1801 [M+H$^+$].

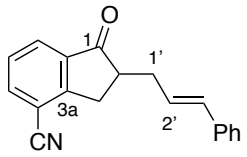
6.4.13. 4-Bromo-2-cinnamyl-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane]



4-Bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (982 mg, 3.00 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (40 mL) and ethylene glycol (3.36 mg, 60.0 mmol, 20 eq), trimethylorthoformate (3.28 mL, 30.0 mmol, 10 eq) and *p*-TsOH·H$_2$O (40.8 mg, 300 μmol, 0.1 eq) were added. The mixture was stirred at RT for 24 h and then heated to reflux for 20 h. The reaction mixture was washed with H_2O (100 mL) and the aq. layer was extracted with CH_2Cl_2 (2x 100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2) to yield the title compound as a colourless oil (675 mg, 61%): R_f 0.19 (CH_2Cl_2/*n*-pentane, 1:2); ν_{max} (neat): 3025w, 2952w, 2888m, 1573w, 1451m, 1314m, 1265m, 1208s, 1049s, 963s, 783s, 747m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 (1H, dd, ^3J 7.9, ^4J 0.8, C5*H*), 7.38–7.34 (2H, m), 7.33–7.28 (2H, m), 7.27–7.24 (1H, m, C7*H*), 7.23–7.19 (1H, m), 7.14–7.10 (1H, m, C6*H*), 6.49 (1H, d, ^3J 15.9, C3'*H*), 6.27 (1H, dt, ^3J 15.8, 7.0, C2'*H*), 4.27–4.07 (4H, OC*H*$_2$C*H*$_2$O), 3.12–3.02 (1H, m, C3*H*), 2.71–2.58 (3H, m, C2*H*, C3*H*, C1'*H*), 2.42–2.33 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.4 (*C*7a), 142.4 (*C*3a), 137.8, 132.4 (*C*5), 131.3 (*C*3'), 129.0 (*C*2'), 128.8 (*C*6), 128.7, 127.2, 126.2, 121.8 (*C*7), 120.8

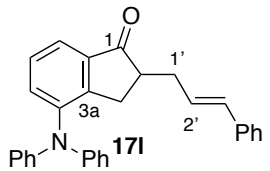
(*C*4), 117.3 (*C*1), 66.0 (O*C*H$_2$CH$_2$O), 65.4 (OCH$_2$*C*H$_2$O), 47.7 (*C*2), 36.0 (*C*3), 32.5 (*C*1'); ESI-MS: m/z calc. for $C_{20}H_{19}BrO_2Na^+$ 393.0461 found 393.0462 [M+Na$^+$].

6.4.14. 2-Cinnamyl-1-oxo-2,3-dihydro-1*H*-indene-4-carbonitrile



4-Bromo-2-cinnamyl-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane] (278 mg, 750 μmol, 1.0 eq) copper cyanide (215 mg, 2.40 mmol, 3.0 eq) and copper iodide (15.2 mg, 75.0 μmol, 0.1 eq) were suspended in DMF (10 mL) and was heated to 140 °C for 42 h. The mixture was cooled to RT, diluted with Et$_2$O (20 mL) and washed with aq. sat. NH$_4$Cl (40 mL). The aq. layer was extracted with Et$_2$O (30 mL) and the combined org. layers were washed with H$_2$O (2x 30 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was dissolved in acetone (30 mL), *p*-TsOH·H$_2$O (15.2 mg, 75.0 μmol, 0.1 eq) was added and the mixture was heated to 70 °C for 2 h. *p*-TsOH·H$_2$O (15.2 mg, 75.0 μmol, 0.1 eq) was added and the mixture was stirred at 70 °C for additional 2 h. The mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (CH$_2$Cl$_2$/*n*-pentane, 1:1 to pure CH$_2$Cl$_2$) to yield the title compound as a white solid (178 mg, 81%, m.p. = 105–107 °C): R_f 0.51 (CH$_2$Cl$_2$); ν_{max} (neat): 2909w, 2361m, 1721s, 1594m, 1497m, 1445w, 1354w, 1266w, 1181w, 982w, 759w, 695w; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.99–7.96 (1H, m, C7*H*), 7.88 (1H, dd, ^3J 7.7, ^4J 1.1, C5*H*), 7.54–7.49 (1H, m, C6*H*), 7.35–7.27 (4H, m), 7.24–7.19 (1H, m), 6.51 (1H, d, ^3J 15.8, C3'*H*), 6.17 (1H, dt, ^3J 15.7, 7.2, C2'*H*), 3.51 (1H, dd, ^2J 18.2, ^3J 8.0, C3*H*), 3.10 (1H, dd, ^2J 18.2, ^3J 4.1, C3*H*), 3.00–2.93 (1H, m, C2*H*), 2.90–2.84 (1H, m, C1'*H*), 2.56–2.47 (1H, m, C1'*H*); ^{13}C NMR (126 MHz, CDCl$_3$) δ = 205.9 (*C*1), 156.6 (*C*3a), 138.0 (*C*5), 137.9 (*C*4), 137.0, 133.2 (*C*3'), 128.7, 128.5 (*C*6), 128.4 (*C*7), 127.6, 126.3, 126.1 (*C*2'), 116.3 (*C*N), 111.6 (*C*7a), 47.2 (*C*2), 34.5 (*C*1'), 31.5 (*C*3); ESI-MS: m/z calc. for $C_{19}H_{15}NONa^+$ 296.1046 found 296.1041 [M+Na$^+$].

6.4.15. 2-Cinnamyl-4-(diphenylamino)-2,3-dihydro-1*H*-inden-1-one (17l)



17l

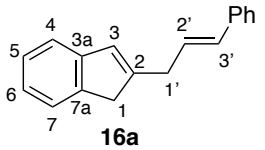
4-Bromo-2-cinnamyl-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane] (371 mg, 1.00 mmol, 1.0 eq), diphenylamine (254 mg, 1.50 mmol, 1.5 eq) and *t*-BuONa (192 mg, 2.00 mmol, 2.0 eq) were suspended in dry toluene (12 mL) and degased with argon for 5 min. $Pd(P(t\text{-}Bu)_3)_2$ (25.6 mg, 50.0 µmol, 5.0 mol%) was added and the mixture was heated to 110 °C for 1 h. After cooling to RT, the mixture was filtered through a plug of silica gel with an upper layer of celite. The plug was rinsed with EtOAc (2x 20 mL). The filtrate was washed with aq. sat. NH_4Cl (20 mL) and the aq. layer was reextratced with EtOAc (2x 20 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in acetone (30 mL) and *p*-TsOH·H_2O (19.0 mg, 100 µmol, 0.1 eq) was added. The black mixture was heated to 50 °C for 1.5 h before concentration *in vacuo* and purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:1 to pure CH_2Cl_2) to yield the title compound **17l** as a brown oil (374 mg, 90%): R_f 0.51(CH_2Cl_2); ν_{max} (neat): 3028w, 2916w, 1710s, 1588m, 1492s, 1278s, 1176w, 1028w, 966m, 909m, 734s, 694s, 626w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.57 (1H, dd, *J* 7.0, 1.6), 7.38–7.31 (2H, m), 7.29–7.24 (2H, m), 7.23–7.14 (7H, m), 7.00–6.94 (6H, m), 6.27 (1H, d, *J* 15.8), 5.97 (1H, dt, *J* 15.8, 7.3), 2.76–2.68 (2H, m), 2.66–2.59 (1H, m), 2.47–2.40 (1H, m), 2.37–2.29 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.5, 150.2, 147.1, 145.3, 139.1, 137.4, 133.1, 132.6, 129.4, 129.1, 128.6, 127.3, 126.5, 126.2, 123.0, 122.8, 120.0, 46.9, 35.0, 30.7; ESI-MS: m/z calc. for$C_{30}H_{25}NONa^+$ 438.1828 found 438.1829 [$M+Na^+$].

6.5. General Procedure C: Reduction and Elimination to Indenes 16

The specified 2-cinnamyl-2,3-dihydro-1*H*-inden-1-one **17** (1.0 eq) was dissolved in MeOH or a mixture of MeOH and MTBE. After cooling to 0 °C, $NaBH_4$ (2.0 eq) was added and the mixture was stirred for the specified time before H_2O (equal amount than solvent) was added and the mixture was extracted with CH_2Cl_2 (2x). The combined org. layers were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in toluene and a catalytic amount of *p*-TsOH·H_2O was added before the mixture was heated to reflux with a Dean-Stark-apparatus for the specified

time. The reaction mixture was cooled to RT and concentrated *in vacuo*. The crude products were purified by column chromatography.

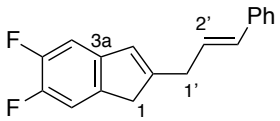
6.5.1. 2-Cinnamyl-1*H*-indene (16a)



16a

Prepared according to the general procedure **C** using 2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (**17a**, 33.8 g, 136 mmol, 1.0 eq) and $NaBH_4$ (10.3 g, 272 mmol, 2.0 eq) in MeOH (500 mL) with a reaction time of 30 min at 0 °C. The elimination was performed using *p*-TsOH·H_2O (259 mg, 1.36 mmol, 1.0 mol%) in toluene (500 mL) with a reaction time of 2.5 h. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) the title compound **16a** was obtained as a slightly yellow oil (29.9 g, 94%): R_f 0.39 (CH_2Cl_2/*n*-pentane , 1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39–7.33 (3H, m), 7.31–7.25 (3H, m), 7.23–7.18 (2H, m), 7.10 (1H, ddd, ^3J 7.4, 7.4, ^4J 1.2), 6.59–6.56 (1H, m, C3*H*), 6.48 (1H, d, ^3J 15.9, C3'*H*), 6.34 (1H, dt, ^3J 15.8, 6.9, C2'*H*), 3.37 (2H, d, ^3J 7.0, C1'*H*), 3.34 (2H, s, C1*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.5, 145.6, 143.4, 137.6, 131.5 (*C*3'), 128.7, 128.0 (*C*2'), 127.4 (*C*3), 127.3, 126.4, 126.2, 124.0, 123.6, 120.3, 41.2 (*C*1), 35.0 (*C*1'). Analytical data is in agreement with the literature.[104]

6.5.2. 2-Cinnamyl-5,6-difluoro-1*H*-indene (16b)

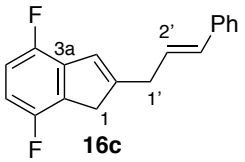


16b

Prepared according to the general procedure **C** using 2-cinnamyl-5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (**17b**, 1.99 g, 7.00 mmol, 1.0 eq) and $NaBH_4$ (530 mg, 14.0 mmol, 2.0 eq) in MeOH/MTBE (50 mL, 4:1) with a reaction time of 30 min at RT. The elimination was performed using *p*-TsOH·H_2O (1.33 mg, 7.00 μmol, 1.0 mol%) in toluene (40 mL) with a reaction time of 2 h. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) the title compound **16b** was obtained as a white solid (1.69 g, 90%, m.p. = 85–87 °C): R_f 0.61 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 3027w, 2891w, 1615m, 1478s, 1362m, 1199w, 1075w, 966w, 873m, 744m, 694m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40–7.34 (2H, m), 7.33–7.28 (2H, m), 7.24–7.20 (1H, m), 7.17–7.12

(1H, m, C7*H*), 7.02 (1H, dd, ^{3}J 7.4, $^{3}J_{H\text{-}F}$ 10.3, C4*H*), 6.52 (2H, m, C3*H*, C2'*H*), 6.31 (1H, dt ^{3}J 15.7, 7.0, C3'*H*), 3.36 (2H, d, ^{3}J 7.0, C1'*H*), 3.31 (2H, s, C1*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 150.2 (d, $^{5}J_{C\text{-}F}$ 4.0, *C*2), 149.9 (dd, $^{1}J_{C\text{-}F}$ 244, $^{2}J_{C\text{-}F}$ 13.7, *C*5), 148.2 (dd, $^{1}J_{C\text{-}F}$ 244, $^{2}J_{C\text{-}F}$ 13.8, *C*6), 141.6 (dd, $^{3}J_{C\text{-}F}$ 7.2, $^{4}J_{C\text{-}F}$ 2.8, *C*4a), 138.9 (dd, $^{3}J_{C\text{-}F}$ 6.6, $^{4}J_{C\text{-}F}$ 3.1, *C*7a), 137.4, 131.9 (*C*2'), 128.7, 127.5, 127.4, 126.3 (*C*3), 112.7 (d, $^{2}J_{C\text{-}F}$ 18.8, *C*7), 108.6 (d, $^{2}J_{C\text{-}F}$ 18.9, *C*4), 41.1 (d, $^{4}J_{C\text{-}F}$ 1.8, *C*3'), 34.9 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –141.7 (1F, m), –145.0 (1F, m); ESI-MS: m/z calc. for $C_{18}H_{13}F_2^-$ 267.0991 found 267.0987 [M–H$^+$].

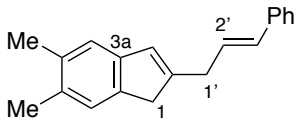
6.5.3. 2-Cinnamyl-4,7-difluoro-1*H*-indene (16c)



16c

Prepared according to the general procedure **C** with 2-cinnamyl-4,7-difluoro-2,3-dihydro-1*H*-inden-1-one (**17c**, 1.31 g, 4.60 mmol, 1.0 eq) and $NaBH_4$ (348 mg, 9.20 mmol, 2.0 eq) in MeOH (50 mL) with a reaction time of 90 min at 0 °C. The elimination was performed using *p*-TsOH·H_2O (1.00 mg, 5.25 μmol, 1.1 mol%) in toluene (80 mL) with a reaction time of 96 h. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:4) the title compound **16c** was obtained as a yellow oil (1.09 g, 89%): R_f 0.52 (CH_2Cl_2/*n*-pentane, 1:4); ν_{max} (neat): 1486s, 1271m, 1226m, 966m, 801m, 732m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40–7.35 (2H, m), 7.33–7.28 (2H, m), 7.25–7.19 (1H, m), 6.87 (1H, ddd, ^{3}J 8.8, 8.7, $^{4}J_{H\text{-}F}$ 3.5, C5*H*), 6.73 (1H, ddd, ^{3}J 8.5, 8.5, $^{4}J_{H\text{-}F}$ 3.5, C6*H*), 6.67–6.64 (1H, m, C3*H*), 6.50 (1H, d, ^{3}J 15.8, C3'*H*), 6.32 (1H, dt, ^{3}J 15.7, 7.0, C2'*H*), 3.42 (2H, s, C1*H*), 3.38 (2H, d, ^{3}J 7.0, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.8 (dd, $^{1}J_{C\text{-}F}$ 241, $^{4}J_{C\text{-}F}$ 2.0, *C*7), 151.8 (dd, $^{1}J_{C\text{-}F}$ 242, $^{4}J_{C\text{-}F}$ 2.0, *C*4), 149.4 (*C*2), 137.3, 134.6 (dd, $^{2}J_{C\text{-}F}$ 18.9, $^{3}J_{C\text{-}F}$ 6.8, *C*4a), 132.2 (*C*3'), 130.4 (dd, $^{2}J_{C\text{-}F}$ 20.7, $^{3}J_{C\text{-}F}$ 6.7, *C*7a), 128.7, 127.5, 127.0 (*C*2'), 126.3, 122.1 (*C*3), 114.7 (dd, $^{2}J_{C\text{-}F}$ 23.1, $^{3}J_{C\text{-}F}$ 7.8, *C*5), 111.9 (dd, $^{2}J_{C\text{-}F}$ 24.0, $^{3}J_{C\text{-}F}$ 7.4, *C*6), 38.5 (*C*1), 34.8 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –125.4 (1F, m), –128.6 (1F, ddd, $^{3}J_{F\text{-}H}$ 22.1, $^{4}J_{F\text{-}H}$ 8.6, $^{5}J_{F\text{-}F}$ 3.5); ESI-MS: m/z calc. for $C_{18}H_{13}F_2^-$ 267.0991 found 267.0989 [M–H$^+$].

6.5.4. 2-Cinnamyl-5,6-dimethyl-1*H*-indene (16d)

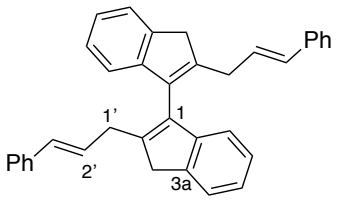


16d

Prepared according to the general procedure **C** using 2-cinnamyl-5,6-dimethyl-2,3-dihydro-1*H*-inden-1-one (**17d**, 614 mg, 2.22 mmol, 1.0 eq) and $NaBH_4$ (168 mg, 4.44 mmol, 2.0 eq) in MeOH (25 mL) with a reaction time of 20 min at 0 °C. The elimination was performed using *p*-TsOH·H_2O (1.00 mg, 5.25 μmol, 0.2 mol%) in toluene (5.0 mL) with a reaction time of 16 h. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) the title compound **16d** was obtained as a slightly yellow oil (453 mg, 78%): R_f 0.65 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025m, 2887m, 1600w, 1450m, 1304w, 965s, 875s, 746s, 694s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37–7.34 (2H, m), 7.32–7.27 (2H, m), 7.22–7.18 (1H, m), 7.15 (1H, s), 7.06 (1H, s), 6.52–6.49 (1H, m), 6.47 (1H, d, *J* 15.7), 6.34 (1H, dt, *J* 15.8, 6.9), 3.36 (2H, d, *J* 6.8), 3.30 (2H, s), 2.27 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.4, 143.4, 141.1, 137.7, 134.4, 132.1, 131.3, 128.7, 128.3, 127.2, 127.2, 126.2, 125.0, 121.5, 40.8, 35.0, 20.1, 20.1.

6.6. Procedures D: Indene Dimerization to Symmetric Biindenes 15

6.6.1. 2,2'-Dicinnamyl-3*H*,3'*H*-1,1'-biindene (15a)

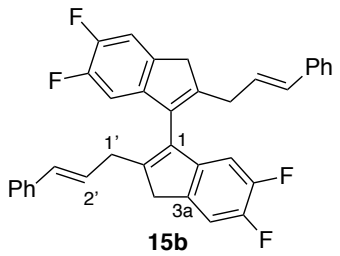


15a

n-BuLi (1.50 molL^{-1} in hexanes, 99.8 mL, 150 mmol, 1.5 eq) was diluted with Et_2O (100 mL) and cooled to –78 °C. A solution of 2-cinnamyl-1*H*-indene (**16a**, 23.2 g, 100 mmol, 1.0 eq) in Et_2O (450 mL) was added dropwise via transfer cannula. The slightly red mixture was stirred at –78 °C for 2:15 h before $CuCl_2$ (16.1 g, 120 mmol, 1.2 eq) was added in one portion and the suspension was warmed to RT. The mixture turned black. After stirring at RT for 18 h, H_2O (200 mL) was slowely added followed by the addition of Et_2O (400 mL) and aq. HCl (1.00 molL^{-1}, 600 mL). The org. layer was separated and the aq. layer was extracted with Et_2O (2x 200 mL). The combined org. layers were washed with aq. HCl (1.00 molL^{-1}, 2x 250 mL). The aq. layer was reextracted

with Et_2O (2x 150 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (475 mL) and pyrrolidine (25 mL) was added. The yellow mixture was stirred at RT for 2.5 h. The mixture was washed with aq. HCl (1.00 $molL^{-1}$, 2x 400 mL) and the aq. layer was reextracted with CH_2Cl_2 (150 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was suspended in MeCN (ca. 100 mL) and filtered to obtain the title compound **15a** as a white solid. The filtrate was concentrated *in vacuo* and flushed through a plug of silica (CH_2Cl_2/*n*-pentane, 1:9). The product fractions were concentrated *in vacuo* and suspended in MeCN. The precipitate was filtered yielding additional **15a** (combined 13.0 g, 56%, m.p. = 169–173 °C): R_f 0.16 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3024w, 2883w, 1600w, 1460m, 1390w, 1305w, 1020w, 964m, 908m, 724s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47–7.44 (2H, m, C4*H*), 7.26–7.21 (8H, m), 7.20–7.15 (6H, m, C5*H*, C6*H*), 7.09–7.05 (2H, m, C7*H*), 6.38 (2H, d, ^3J 15.7, C3'*H*), 6.21 (2H, dt, ^3J 15.7, 6.9, C2'*H*), 3.58 (4H, d, ^4J 2.4, C3*H*), 3.32 (4H, d, ^3J 6.9, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.2 (*C*7a), 144.9 (*C*2), 143.0 (*C*3a), 137.5, 133.6 (*C*1), 131.3 (*C*3'), 128.6, 128.3 (*C*2'), 127.2, 126.4 (*C*6), 126.2, 124.4 (*C*5), 123.6 (*C*4), 120.3 (*C*7), 41.0 (*C*3), 33.6 (*C*1'); ESI-MS: m/z calc. for $C_{36}H_{29}^-$ 461.2275 found 461.2267 [M–H$^+$].

6.6.2. 2,2'-Dicinnamyl-5,5',6,6'-tetrafluoro-3*H*,3'*H*-1,1'-biindene (15b)

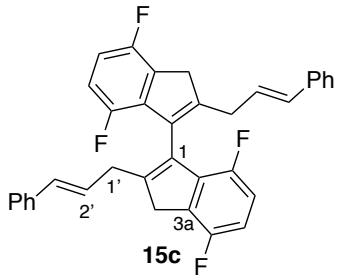


15b

n-BuLi (1.59 mL^{-1} in hexanes, 5.66 mL, 9.00 mmol, 1.5 eq) was diluted with Et_2O (5.0 mL) and cooled to –78 °C. A solution of 2-cinnamyl-5,6-difluoro-1*H*-indene (**16b**, 1.61 g, 6.00 mmol, 1.0 eq) in Et_2O (15 mL) was added dropwise. The mixture turned maroon red and a precipitation formed. The suspension was stirred at –78 °C for 1.5 h before $CuCl_2$ (968 mg, 7.20 mmol, 1.2 eq) was added in one portion and the cooling bath was removed and the mixture turned black while warming up. After stirring at RT for 15 h, aq. HCl (1.00 mL^{-1}, 20 mL) was added. The org. layer was decanted and washed again with aq. HCl (1.00 mL^{-1}, 20 mL). The combined aq. layers were reextracted with Et_2O (2x 30 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), pyrrolidine (100 µL)

was added and the mixture was stirred at RT for 3 h. The reaction mixture was washed with aq. HCl (1.00 mL^{-1}, 2x 10 mL). The combined aq. layers were reextracted with CH_2Cl_2 (2x 20 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:4) to yield the title compound **15b** as a slightly yellow oil (817 mg, 51%): R_f 0.24 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3027w, 2901, 1604m, 1479s, 1348m, 1282m, 1156m, 1092m, 964m, 867s, 791m, 728s, 690s, 621m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.22–7.06 (12H, m, C4*H*), 6.69 (2H, dd, ^3J 7.3, $^3J_{H\text{-}F}$ 10.3, C7*H*), 6.29 (2H, d, ^3J 15.7, C3'*H*), 6.08 (2H, d, ^3J 15.7, 7.0, C2'*H*), 3.52–3.39 (4H, m, C3*H*), 3.25–3.15 (4H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 150.1 (dd, $^1J_{C\text{-}F}$ 245, $^2J_{C\text{-}F}$ 13.8, *C*5/*C*6), 148.8 (dd, $^1J_{C\text{-}F}$ 245, $^2J_{C\text{-}F}$ 13.9, *C*5/*C*6), 147.0 (d, $^5J_{C\text{-}F}$ 4.0, *C*2), 141.9 (dd, $^3J_{C\text{-}F}$ 6.6, $^4J_{C\text{-}F}$ 2.5, *C*7a), 138.3 (dd, $^3J_{C\text{-}F}$ 6.8, $^4J_{C\text{-}F}$ 3.2, *C*3a), 137.2, 131.9 (*C*3'), 131.9, 128.7, 127.5, 127.2 (*C*2'), 126.2, 112.9 (d, ^2J 19.0, *C*4), 108.3 (d, $^2J_{C\text{-}F}$ 19.0, *C*7), 40.9 (d, $^4J_{C\text{-}F}$ 1.4, *C*3), 33.6 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –140.9 (2F, m), –143.2 (2F, m); ESI-MS: m/z calc. for $C_{36}H_{26}F_4Na^+$ 557.1863 found 557.2853 [M+Na^+].

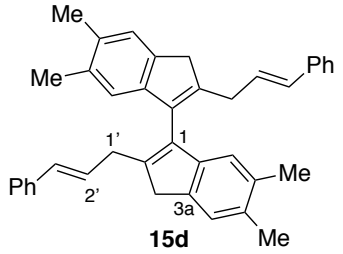
6.6.3. 2,2'-Dicinnamyl-4,4',7,7'-tetrafluoro-3*H*,3'*H*-1,1'-biindene (15c)



n-BuLi (1.50 mL^{-1} in hexanes, 2.50 mL, 3.75 mmol, 1.5 eq) was diluted in Et_2O (8.0 mL) and cooled to –78 °C. A solution of 2-cinnamyl-4,7-difluoro-1*H*-indene (**16c**, 671 mg, 2.50 mmol, 1.0 eq) in Et_2O (32 mL) was added dropwise. The orange/reddish solution was stirred at –78 °C for 2 h, before $CuCl_2$ (403 mg, 4.00 mmol, 1.6 eq) was added in one portion and the mixture was warmed to RT. The mixture turned black while warming up. After stirring at RT for 17 h, aq. HCl (1.00 mL^{-1}, 20 mL) was added and the org. layer was separated. The aq. layer was extracted with Et_2O (30 mL) and the combined org. layers were washed with H_2O (30 mL). The aq. layer was extraced with Et_2O (20 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), pyrrolidine (200 µL) was added and the mixture was stirred at RT for 30 min. The reaction mixture was washed with aq. HCl (1.00 mL^{-1},

10 mL). The org. layer was separated and the aq. layer was reextracted with CH_2Cl_2 (2x 10 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was suspended in MeCN (15 mL) and filtered to yield the title compound **15c** as a white solid. The filtrate was purified by column chromatography (*n*-pentane/toluene, 4:1) to yield additional **15c** (combined 313 mg, 47%, m.p. = 162 °C): R_f 0.49 (*n*-pentane/CH_2Cl_2, 4:1); ν_{max} (neat): 1448s, 1250m, 972m, 806s, 731s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31–7.12 (10H, m), 6.89–6.73 (4H, m, C5*H*, C6*H*), 6.40 (2H, d, ^3J 15.9, C2'*H*), 6.18 (2H, dt, ^3J 15.7, 6.9, C3'*H*), 3.67–3.54 (4H, m, C3*H*), 3.37–3.24 (4H, m, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.8 (dd, $^1J_{C\text{-}F}$ 241, $^4J_{C\text{-}F}$ 2.3, *C*4), 152.5 (dd, $^1J_{C\text{-}F}$ 244, $^4J_{C\text{-}F}$ 2.0, *C*7), 145.8, 137.2, 135.1 (m, *C*3a/*C*7a), 131.9 (*C*2'), 130.4, 129.9 (dd, $^2J_{C\text{-}F}$ 21.6, $^3J_{C\text{-}F}$ 5.9, *C*3a/*C*7a), 128.7, 127.4, 127.0 (*C*3'), 126.2, 115.2 (dd, $^2J_{C\text{-}F}$ 23.5, $^3J_{C\text{-}F}$ 7.9, *C*5/*C*6), 112.2 (dd, $^2J_{C\text{-}F}$ 23.8, $^3J_{C\text{-}F}$ 7.5, *C*5/*C*6), 38.1 (*C*3'), 33.0 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –125.8 (2F, ddd, $^3J_{F\text{-}H}$ 21.5, $^4J_{F\text{-}H}$ 8.0, $^5J_{F\text{-}F}$ 3.6), –129.8 (2F, ddd, $^3J_{F\text{-}H}$ 21.7, $^4J_{F\text{-}H}$ 9.3, $^5J_{F\text{-}F}$ 3.3); ESI-MS: m/z calc. for $C_{36}H_{25}F_4^-$ 533.1898 found 533.1890 [M–H$^+$].

6.6.4. 2,2'-Dicinnamyl-5,5',6,6'-tetramethyl-3*H*,3'*H*-1,1'-biindene (15d)



15d

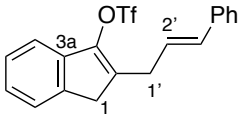
n-BuLi (1.59 molL^{-1} in hexanes, 1.51 mL, 2.40 mmol, 1.5 eq) was diluted with Et_2O (1.0 mL) and cooled to –78 °C. A solution of 2-cinnamyl-5,6-dimethyl-1*H*-indene (**16d**, 417 mg, 1.60 mmol, 1.0 eq) in Et_2O (7.0 mL) was added dropwise. The slightly orange mixture was stirred at –78 °C for 2 h before $CuCl_2$ (258 mg, 1.92 mmol, 1.2 eq) was added in one portion and the suspension was warmed to RT whereby the mixture turned black. After stirring at RT for 5 h, aq. HCl (1.00 molL^{-1}, 5.0 mL) was added. The org. layer was separated and washed with aq. HCl (1.00 molL^{-1}, 5.0 mL). The aq. layer was reextracted with Et_2O (2x 5.0 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was flushed through a plug of silica with Et_2O (50 mL) and the filtrate was concentrated *in vacuo.* The residue was dissolved in pyrrolidine (2.0 mL) and stirred at RT for 3.5 h. Aq. HCl (1.00 molL^{-1}, 10 mL) and CH_2Cl_2 (10 mL) were added. The org. layer was separated and the aq. layer was reextracted with CH_2Cl_2 (2x 10 mL). The combined org. layers concentrated *in vacuo* to a volume of approximately 5.0 mL and

was flushed through a plug of silica with Et_2O (20 mL). The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:9) to yield the title compound **15d** as an orange oil (115 mg, 28%): R_f 0.43 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3024m, 2924m, 2362w, 1602w, 1453m, 1393w, 1028w, 965m, 863m, 749m, 699s; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29–7.23 (6H, m), 7.21–7.15 (6H, m), 6.88 (2H, s), 6.39 (2H, d, *J* 15.6), 6.05 (2H, dt, *J* 15.6, 7.3), 3.67 (4H, s), 3.43 (4H, d, *J* 7.3), 2.30 (6H, s), 2.20 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2, 142.3, 140.7, 140.0, 134.6, 133.5, 129.9, 128.7, 128.6, 127.2, 126.2, 125.1, 122.1, 39.9, 37.6, 20.1, 20.0.

6.7. General Procedure E: Formation of Enol Triflates 23

The specified 2-cinnamyl-2,3-dihydro-1*H*-inden-1-one **17** (1.0 eq) was dissolved in CH_2Cl_2 and *i*-Pr_2NEt (1.2 eq) was added followed by the dropwise addition of Tf_2O (1.25 eq). The resulting mixture was stirred at the specified temperature before the reaction mixture was washed with H_2O (equal amount as solvent). The aq. layer was reextracted with CH_2Cl_2 (2x), the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography.

6.7.1. 2-Cinnamyl-1*H*-inden-3-yl trifluoromethanesulfonate (23a)

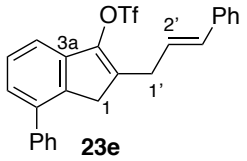


23a

Prepared according to the general procedure **E** using 2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (**17a**, 24.8 g, 100 mmol, 1.0 eq), *i*-Pr_2NEt (19.8 mL, 120 mmol, 1.2 eq) and Tf_2O (20.7 mL, 125 mmol, 1.25 eq) in CH_2Cl_2 (500 mL) with a reaction time of 4 h at RT. Column chromatography (CH_2Cl_2/*n*-pentane, 1:9) yielded the title compound **23a** as a slightly yellow oil (26.2 g, 69%): R_f 0.47 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 3029w, 1640w, 1418m, 1208s, 1137s, 1041m, 966m, 847s, 750m, 723m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40–7.32 (5H, m), 7.32–7.27 (2H, m), 7.26–7.20 (2H, m), 6.53 (1H, d, ^3J 15.7, C3'*H*), 6.21 (1H, dt, ^3J 15.7, 7.1, C2'*H*), 3.48–3.42 (4H, m, C1*H*, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.3, 139.7, 137.5, 137.0, 134.9, 132.9 (*C*3'), 128.7, 127.7, 127.1, 126.4, 126.2, 125.5 (*C*2'), 124.3, 118.8 (q, $^1J_{C\text{-}F}$ 320, *C*F_3), 118.0, 37.5 (*C*1),

30.7 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –73.5 (3F, s); ESI-MS: m/z calc. for $C_{19}H_{15}F_3O_3SNa^+$ 403.0586 found 403.0588 [$M+Na^+$].

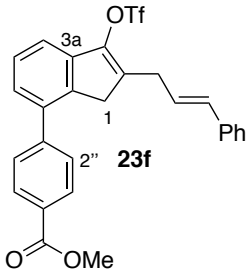
6.7.2. 2-Cinnamyl-7-phenyl-1*H*-inden-3-yl trifluoromethanesulfonate (23e)



23e

Prepared according to the general procedure **E** using 2-cinnamyl-4-phenyl-2,3-dihydro-1*H*-inden-1-one (**17e**, 1.14 g, 3.50 mmol, 1.0 eq), *i*-Pr_2NEt (694 µL, 4.20 mmol, 1.2 eq) and Tf_2O (726 µL, 4.38 mmol, 1.25 eq) in CH_2Cl_2 (50 mL) with a reaction time of 17.5 h at 40 °C. Column chromatography (CH_2Cl_2/*n*-pentane, 1:9) yielded the title compound **23e** as a slightly yellow oil (1.09 g, 68%): R_f 0.41 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 3029w, 1419m, 1209s, 1137s, 1046m, 965m, 853s, 696m, 612m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47–7.41 (5H, m), 7.38–7.34 (2H, m), 7.34–7.31 (2H, m), 7.31–7.26 (3H, m), 7.23–7.19 (1H, m), 6.50 (1H, d, ^3J 15.8, C3'*H*), 6.20 (1H, dt, ^3J 15.7, 7.0, C2'*H*), 3.51 (2H, s, C1*H*), 3.45 (2H, d, ^3J 7.1, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.2, 139.9, 138.4, 138.0, 137.2, 137.0, 135.1, 132.9, 128.8, 128.7, 128.6, 127.9, 127.7, 127.7, 127.1, 126.4, 125.4 (*C*2'), 118.8 (q, $^1J_{C\text{-}F}$ 320, *C*F_3), 117.1, 37.4 (*C*1), 30.7 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –73.4 (3F, s).

6.7.3. Methyl 4-(2-cinnamyl-3-(((trifluoromethyl)sulfonyl)oxy)-1*H*-inden-7-yl)benzoate (23f)

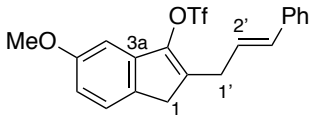


23f

Methyl 4-(2-cinnamyl-1-oxo-2,3-dihydro-1*H*-inden-4-yl)benzoate (**17f**, 223 mg, 560 µmol, 1.0 eq) was dissolved in CH_2Cl_2 (15 mL) and 2,6-di-*tert*-butylpyridine (151 µL, 672 µmol, 1.2 eq) was added followed by the addition of Tf_2O (116 µL, 700 µmol, 1.25 eq). The mixture was stirred at RT for 4 h before H_2O (20 mL) was added and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 20 mL) and the combined org. layers were dried over Na_2SO_4,

filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:1) to yield the title compound **23f** as a slightly yellow oil (189 mg, 66%): R_f 0.18 (CH_2Cl_2/*n*-pentane, 1:4); ν_{max} (neat): 2927w, 1723m, 1611w, 1423m, 1281s, 1214s, 1139s, 1046w, 967w, 856m, 769w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13–8.10 (2H, m, C3''*H*, C5''*H*), 7.55–7.52 (2H, m), 7.49–7.44 (1H, m), 7.40 (1H, d, *J* 7.6), 7.35–7.26 (5H, m), 7.24–7.19 (1H, m), 6.51 (1H, d, ^3J 15.8, C3'*H*), 6.19 (1H, dt, ^3J 15.7, 7.0, C2'*H*), 3.94 (3H, s, CO_2CH_3), 3.49 (2H, s, C3*H*), 3.46 (2H, d, ^3J 7.1, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.8 (*C*O_2CH$_3$), 144.3 (*C*4''), 142.0, 138.1, 137.2, 137.0, 136.7, 135.2, 132.9 (*C*3'), 130.0 (*C*3'', *C*5''), 129.3, 128.6, 128.5 (*C*2'', *C*6''), 127.9, 127.6, 126.7, 126.2, 125.0 (*C*2'), 118.7 ($J_{C\text{-}F}$ 320, *C*F_3), 117.7, 52.2 (CO_2CH_3), 37.2 (*C*3), 30.6 (*C*1'),^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.4 (3F, s); ESI-MS: m/z calc. for $C_{27}H_{21}F_3O_3SNa^+$ 537.0954 found 537.0939 [M+Na$^+$].

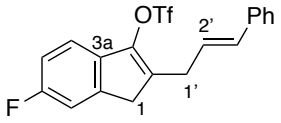
6.7.4. 2-Cinnamyl-5-methoxy-1*H*-inden-3-yl trifluoromethanesulfonate (23g)



23g

Prepared according to general procedure **E** using 2-cinnamyl-6-methoxy-2,3-dihydro-1*H*- inden-1-one (**17g**, 640 mg, 2.30 mmol, 1.0 eq), *i*-Pr_2NEt (456 µL, 2.76 mmol, 1.2 eq) and Tf_2O (477 µL, 2.88 mmol, 1.25 eq) in CH_2Cl_2 (20 mL) with a reaction time of 20 h at 40 °C. Column chromatography (CH_2Cl_2/*n*-pentane, 1:4) yielded the title compound **23g** as a slightly yellow oil (441 mg, 48%): R_f 0.15 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 3028w, 1614w, 1483m, 1417m, 1206s, 1137s, 1030m, 966m, 845m, 748m, 693m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37–7.33 (2H, m), 7.32–7.28 (2H, m), 7.27–7.20 (2H, m, C7*H*), 6.89 (1H, d, ^4J 2.4, C4*H*), 6.79 (1H, dd, ^3J 8.2, ^4J 2.4, C6*H*), 6.52 (1H, d, ^3J 15.8, C3'*H*), 6.21 (1H, dt, ^3J 15.7, 7.1, C2'*H*), 3.83 (3H, s, OCH_3), 3.44 (2H, d, ^3J 7.1, C1'*H*), 3.39 (2H, s, C1*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.4 (*C*5), 142.0 (*C*3), 138.8 (*C*3a), 137.0, 136.4 (*C*2), 132.9 (*C*3') 131.9 (*C*7a), 128.7, 127.7, 126.4, 125.5 (*C*2'), 124.9 (*C*7), 118.8 (q, $^1J_{C\text{-}F}$ 320, *C*F_3), 112.4 (*C*6), 103.6 (*C*4), 55.7 (O*C*H$_3$), 36.8 (*C*1), 30.8 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –73.5 (3F, s); ESI-MS: m/z calc. for $C_{20}H_{17}F_3O_4SNa^+$ 433.0692 found 433.0689 [M+Na$^+$].

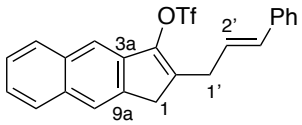
6.7.5. 2-Cinnamyl-6-fluoro-1*H*-inden-3-yl trifluoromethanesulfonate (23h)



23h

Prepared according to general procedure **E** using 2-cinnamyl-5-fluoro-2,3-dihydro-1*H*-inden-1-one (**17h**, 639 mg, 2.40 mmol, 1.0 eq), *i*-Pr_2NEt (476 µL, 2.88 mmol, 1.2 eq) and Tf_2O (498 µL, 3.00 mmol, 1.25 eq) in CH_2Cl_2 (40 mL) with a reaction time of 17.5 h at 40 °C. Column chromatography (CH_2Cl_2/*n*-pentane, 1:9) yielded the title compound **23h** as a slightly yellow oil (555 mg, 58%): R_f 0.46 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 1615w, 1477w, 1419m, 1355w, 1208s, 1137s, 1057m, 967m, 843s, 752m, 692m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38–7.33 (2H, m), 7.33–7.26 (3H, m), 7.26–7.21 (1H, m), 7.10 (1H, dd, $^3J_{H-F}$ 8.4, ^4J 2.2, C7*H*), 7.08–7.02 (1H, m, C5*H*), 6.53 (1H, d, ^3J 15.8, C3'*H*), 6.21 (1H, dt, ^3J 15.8, 6.9, C2'*H*), 3.46–3.41 (4H, m, C1*H*, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.2 (d, $^1J_{C-F}$ 245, *C*6), 141.8 (d, $^3J_{C-F}$ 8.9), 141.5 (d, $^5J_{C-F}$ 0.9), 136.9, 134.5 (d, $^4J_{C-F}$ 3.9), 133.5 (d, $^4J_{C-F}$ 2.3, *C*3a), 133.1 (*C*3'), 128.8, 127.8, 126.4, 125.3 (*C*2'), 119.0 (d, $^3J_{C-F}$ 8.9), 118.8 (q, $^1J_{C-F}$ 320, *C*F_3), 114.3 (d, $^2J_{C-F}$ 23.3, *C*5), 112.3 (d, $^2J_{C-F}$ 23.8, *C*7), 37.4 (d, $^4J_{C-F}$ 2.3, *C*1), 30.7 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$): δ = –73.5 (3F, s); ESI-MS: m/z calc. for $C_{19}H_{14}F_4O_3SNa^+$ 421.0492 found 421.0485 [$M+Na^+$].

6.7.6. 2-Cinnamyl-1*H*-cyclopenta[*b*]naphthalen-3-yl trifluoromethanesulfonate (23i)

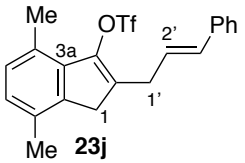


23i

Prepared according to general procedure **E** using 2-cinnamyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (**17i**, 835 mg, 2.80 mmol, 1.0 eq), *i*-Pr_2NEt (555 µL, 3.36 mmol, 1.2 eq) and Tf_2O (581 µL, 3.50 mmol, 1.25 eq) in CH_2Cl_2 (28 mL) with a reaction temperature of 24 h at 40 °C. Column chromatography (CH_2Cl_2/*n*-pentane, 1:9) yielded the title compound **23i** as a brown oil (751 mg, 59%): R_f 0.50 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3029w, 2363w, 1633w, 1497w, 1417m, 1312w, 1211s, 1139s, 1029m, 966m, 847s, 749m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91–7.86 (1H, m), 7.82–7.78 (1H, m), 7.75 (1H, s), 7.73 (1H, s), 7.49–7.42 (2H, m), 7.39–7.34

(2H, m), 7.33–7.27 (2H, m), 7.25–7.20 (1H, m), 6.56 (1H, d, *J* 15.7), 6.24 (1H, dt, *J* 15.7, 7.1), 3.55 (2H, s), 3.48 (2H, d, *J* 7.1); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.3, 137.0, 136.7, 136.6, 136.0, 133.2, 132.8, 132.4, 128.8, 128.5, 128.0, 127.7, 126.4, 126.1, 126.0, 125.1, 123.2, 118.8 (q, $J_{C\text{-}F}$ 320), 115.0, 36.8, 31.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.4 (3F); ESI-MS: m/z calc. for $C_{23}H_{17}F_3O_3SNa^+$ 453.0743 found 453.0739 [M+Na$^+$].

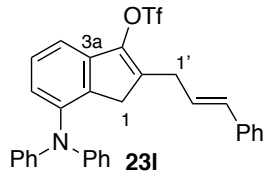
6.7.7. 2-Cinnamyl-4,7-dimethyl-1*H*-inden-3-yl trifluoromethanesulfonate (23j)



23j

Prepared according to general procedure **E** using 2-cinnamyl-4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (**17j**, 719 mg, 2.60 mmol, 1.0 eq), *i*-Pr_2NEt (516 µL, 3.12 mmol, 1.2 eq) and Tf_2O (539 µL, 3.25 mmol, 1.25 eq) in CH_2Cl_2 (30 mL) with a reaction time of 21 h at 40 °C. Column chromatography (CH_2Cl_2/*n*-pentane, 1:9) yielded the title compound **23j** as an orange oil (821 mg, 77%): R_f 0.59 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3028w, 1498w, 1403m, 1213s, 1140m, 1053w, 967w, 860m, 749w, 694w, 636w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40–7.35 (2H, m), 7.34–7.28 (2H, m), 7.25–7.21 (1H, m), 7.00 (1H, d, *J* 7.8), 6.95 (1H, d, *J* 7.8), 6.55 (1H, d, *J* 15.8), 6.25 (1H, dt, *J* 15.8, 7.0), 3.48 (2H, d, *J* 7.1), 3.27 (2H, s), 2.52 (3H, s), 2.25 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.1, 138.7, 137.1, 135.1, 134.9, 132.8, 130.8, 130.2, 128.7, 127.7, 127.4, 127.3, 126.4, 126.0, 118.7 (q, $J_{C\text{-}F}$ 320), 36.2, 31.2, 18.2, 17.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.5 (3F); ESI-MS: m/z calc. for $C_{21}H_{19}F_3O_3SNa^+$ 431.0899 found 431.0891 [M+Na$^+$].

6.7.8. 2-Cinnamyl-7-(diphenylamino)-1*H*-inden-3-yl trifluoromethanesulfonate (23l)



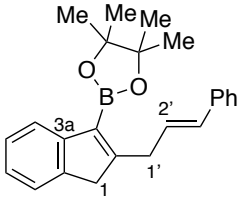
23l

Prepared according to general procedure **E** using 2-cinnamyl-4-(diphenylamino)-2,3-dihydro-1*H*-inden-1-one (**17l**, 125 mg, 300 µmol, 1.0 eq), *i*-Pr_2NEt (59.5 µL, 360 µmol, 1.2 eq) and Tf_2O (62.2 µL, 375 µmol, 1.25 eq) in CH_2Cl_2 (10 mL) with a reaction time of 24 h at RT. Column

chromatography (CH_2Cl_2/*n*-pentane, 1:4) yielded the title compound **23l** as a colourless oil (79.1 mg, 48%): R_f 0.59 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 3030w, 2925w, 1585m, 1493m, 1422m, 1296m, 1212s, 1139s, 1096w, 1014w, 967w, 850m, 752m, 695m, 619m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32–7.26 (5H, m), 7.24–7.19 (5H, m), 7.16 (1H, d, ^3J 7.5, C4*H*), 7.05 (1H, dd, ^3J 8.1, ^4J 0.8, C6*H*), 7.02–6.98 (4H, m), 6.98–6.94 (2H, m), 6.39 (1H, d, ^3J 15.8, C3'*H*), 6.07 (1H, dt, ^3J 15.8, 7.0, C2'*H*), 3.31 (2H, d, ^3J 7.1, C1'*H*), 2.87 (2H, s, C1*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.2, 143.0, 141.5 (*C*3), 139.5, 137.0, 135.1, 134.3 (*C*7a), 132.8 (*C*3'), 129.4, 128.8, 128.6, 127.6, 126.3, 125.3 (*C*2'), 125.0 (*C*6), 123.2, 122.7, 118.8 (q, $^1J_{C\text{-}F}$ 320, *C*F_3), 114.6 (*C*4), 36.7 (*C*1), 30.4 (*C*1'); ^{19}F NMR (471 MHz, $CDCl_3$): δ = –73.47 (3F, s); ESI-MS: m/z calc. for $C_{31}H_{25}F_3NO_3S^+$ 548.1502 found 548.1494 [$M+H^+$].

6.8. Miyaura-borylation and Formation of Trifluoroborate Salt 25

6.8.1. 2-(2-Cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24) [118]

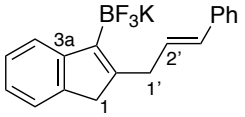


24

A two-necked flask was charged with 2-cinnamyl-1*H*-inden-3-yl trifluoromethanesulfonate (**23a**, 5.71 g, 15.0 mmol, 1.0 eq), bis(pinacolato)diboron (4.57 g, 18.0 mmol, 1.2 eq) and KOAc (3.68 g, 37.5 mmol, 2.5 eq). Toluene (120 mL) was added and the suspension was degased with argon for 10 min before $Pd(PPh_3)_4$ (867 mg, 750 µmol, 5.0 mol%) was added and the brown mixture was heated to 80 °C for 4.5 h. H_2O (200 mL) and EtOAc (100 mL) were added. The org. layer was separated and the aq. layer was extracted with EtOAc (100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:4) to yield the title compound **24** as a white solid (4.17 g, 78%, m.p. = 110–111 °C): R_f 0.15 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 2974w, 1570w, 1460m, 1384s, 1316m, 1141s, 985m, 856m, 768s, 747m, 688s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (1H, d, ^3J 7.7, C4*H*), 7.36–7.31 (3H, m), 7.30–7.22 (3H, m), 7.21–7.16 (1H, m), 7.09 (1H, ddd, ^3J 7.4, 7.4, ^4J 1.1, C6*H*), 6.48 (1H, d, ^3J 15.7, C3'*H*), 6.31 (1H, dt, ^3J 15.7, 7.1, C2'*H*), 3.72 (2H, dd, ^3J

7.1, ^4J 1.0, C1'*H*), 3.46 (2H, s, C1*H*), 1.36 (12H, 4x CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.8 (*C*2), 148.4, 143.0 (*C*7a), 131.0 (*C*3'), 129.3 (*C*2'), 128.6, 127.1, 126.4, 126.2, 123.9 (*C*6), 123.2, 122.4 (*C*4), 83.2 (O*C*$(CH_3)_2$), 43.4 (*C*1), 35.1 (*C*1'), 25.1 (*C*H_3); ESI-MS: m/z calc. for $C_{24}H_{28}BO_2^+$ 359.2181 found 359.2177 [$M+H^+$].

6.8.2. (2-Cinnamyl-1*H*-inden-3-yl)trifluoro-borane potassium salt (25)



25

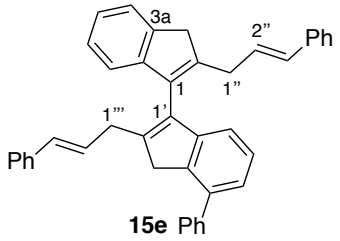
A Falcon® tube was charged with 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**, 1.43 g, 4.00 mmol, 1.0 eq) and MeOH (30 mL). A solution of KHF_2 (2.19 g, 28.0 mmol, 7.0 eq) in H_2O (7.0 mL) was added and the mixture was stirred at RT for 1.5 h. The solvent was removed under reduced pressure, the residue was dissolved in refluxing MeCN (40 mL) and filtered. The slightly yellow filtrate was cooled to RT, concentrated *in vacuo* and Et_2O (10 mL) was added. The precipitation was filtered and washed with Et_2O (2x 5.0 mL) to yield the title compound **25** as a white powder (1.10 g, 81%, m.p. = 152 °C (decomp)): R_f 0.08 (CH_2Cl_2/MeOH, 20:1); ν_{max} (neat): 3024w, 1706w, 1593m, 1457m, 1332w, 1189w, 1111m, 1014s, 953s, 882s, 742s, 727s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (1H, d, ^3J 7.5, C4*H*), 7.38–7.34 (2H, m), 7.30–7.25 (2H, m), 7.21 (1H, d, ^3J 7.2, C7*H*), 7.19–7.14 (1H, m), 7.05–7.00 (1H, m, C5*H*), 6.86 (1H, ddd, ^3J 7.4, 7.4, ^4J 1.2, C6*H*), 6.43–6.32 (2H, m, C2'*H*, C3'*H*), 3.47 (2H, d, ^3J 5.6, C1*H*), 3.11 (2H, s, C1'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 152.1 (*C*4a), 145.6 (*C*2), 143.4 (*C*7a), 137.6, 131.3 (*C*2/*C*3'), 128.9 (*C*2/*C*3'), 128.5, 126.6, 125.7, 125.0 (*C*5), 122.4 (*C*4), 122.0 (*C*7), 121.6 (*C*6), 41.4 (*C*1'), 34.1 (*C*1); ^{19}F NMR (471 MHz, $CDCl_3$) δ = –133.7 (3F, br s); ESI-MS: m/z calc. for $C_{18}H_{15}BF_3^-$ 299.1228 found 299.1225 [$M–K^+$].

6.9. General Procedure F: Suzuki-Miyaura Coupling

The specified triflate **23** (1.0 eq), trifluoro-borane potassium salt **25** or 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **24** (1.1 eq), Cs_2CO_3 (0.8 eq), KF (2.4 eq) and PPh_3 (0.1 eq) were suspended in a mixture of THF and H_2O (9:1). The suspension was degassed with argon in the ultrasonic bath for 15 min before (dppf)$PdCl_2$ (8.0 mol%) was added and the mixture stirred at 80 °C for the specified time. After cooling to RT, H_2O and Et_2O were added and the org.

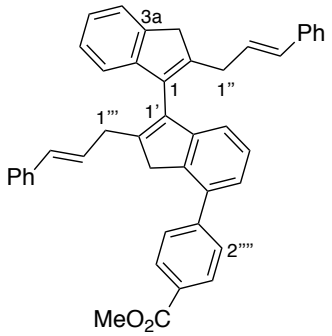
layer was separated. The aq. layer was reextracted with Et_2O (2x). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

6.9.1. 2,2'-Dicinnamyl-4-phenyl-3*H*,3'*H*-1,1'-biindene (15e)



Performed according to general procedure **F** using 2-cinnamyl-7-phenyl-1*H*-inden-3-yl trifluoromethanesulfonate (**23e**, 288 mg, 500 µmol, 1.0 eq), 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**, 197 mg, 550 µmol, 1.1 eq), Cs_2CO_3 (130 mg, 400 µmol, 0.8 eq), KF (69.7 mg, 1.20 mmol, 2.4 eq), PPh_3 (13.1 mg, 50.0 µmol, 0.1 eq) and $(dppf)PdCl_2$ (29.3 mg, 40.0 µmol, 8.0 mol%) in a mixture of THF/H_2O (15 mL, 9:1) with a reaction time of 17 h at 80 °C. The crude product was purified by column chromatography (*n*-pentane/toluene, 4:1) to yield the title compound **15e** as slightly yellow oil (86.5 mg, 32%): R_f 0.13 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 2886w, 1597w, 1463m, 1307w, 1074w, 1026w, 965m, 908m, 728s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59–7.54 (2H, m), 7.49–7.43 (3H, m), 7.39–7.34 (1H, m), 7.31–7.27 (1H, m), 7.26–7.13 (13H, m), 7.13–7.09 (1H, m), 7.09–7.05 (1H, dd, ^3J 7.5, ^4J 1.0), 6.39 (1H, d, ^3J 15.7), 6.35 (1H, d, ^3J 15.8), 6.27–6.14 (2H, m), 3.67–3.56 (4H, m), 3.34 (2H, d, ^3J 6.9), 3.31 (2H, d, ^3J 6.8); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.7, 146.2, 145.2, 145.0, 143.0, 141.3, 140.4, 137.8, 137.5, 137.5, 133.6, 133.6, 131.3, 131.3, 128.7, 128.6, 128.6, 128.6, 128.3, 128.1, 127.3, 127.2, 127.2, 127.2, 126.4, 126.2, 126.2, 125.2, 124.4, 123.7, 120.3, 119.5, 41.1, 41.0, 33.6, 33.6; ESI-MS: m/z calc. for $C_{42}H_{33}^-$ 537.2588 found 537.2581 [M–H$^+$].

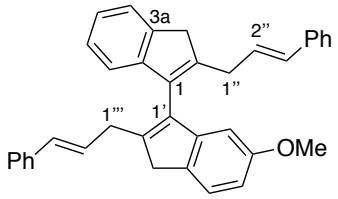
6.9.2. Methyl 4-(2,2'-dicinnamyl-3*H*,3'*H*-[1,1'-biinden]-4-yl)benzoate (15f)



15f

Performed according to general procedure **F** using methyl 4-(2-cinnamyl-3-(((trifluoromethyl)sulfonyl)oxy)-1*H*-inden-7-yl)benzoate (**23f**, 185 mg, 360 µmol, 1.0 eq), 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**, 142 mg, 396 µmol, 1.1 eq), Cs_2CO_3 (93.8 mg, 288 µmol, 0.8 eq), KF (50.2 mg, 864 µmol, 2.4 eq), PPh_3 (9.44 mg, 36.0 µmol, 0.1 eq) and (dppf)$PdCl_2$ (21.1 mg, 28.8 µmol, 8.0 mol%) in a mixture of THF/H_2O (10 mL, 9:1) with a reaction time of 20 h at 80 °C. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:1) to yield the title compound **15f** as slightly yellow oil (135 mg, 63%): R_f 0.46 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3025w, 1720s, 1609w, 1435w, 1393w, 1278s, 1181w, 1113m, 1019w, 965m, 908m, 728s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14–8.11 (2H, m, C3’’’’*H*), 7.65–7.61 (2H, m, C2’’’’*H*), 7.47 (1H, d, *J* 6.9), 7.33–7.28 (1H, m), 7.25–7.13 (12H, m), 7.12–7.07 (3H, m), 6.41–6.32 (2H, m), 6.26–6.13 (2H, m), 3.93 (3H, m, CO_2CH_3), 3.65–3.54 (4H, m, C3*H*, C3’*H*), 3.34 (2H, d, ^3J 6.9, C1’’*H*/C1’’’*H*), 3.31 (2H, d, ^3J 6.9, C1’’*H*/C1’’’*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.1 (CO_2CH_3), 146.9, 146.1, 146.0 (*C*1’’’’), 145.3, 145.1, 142.9, 140.4, 137.4, 137.4, 136.7, 133.6, 133.4, 131.4, 131.3, 129.9 (*C*3’’’’), 128.9, 128.6, 128.6, 128.6, 128.1, 127.9, 127.3, 127.2, 127.2, 126.4, 126.1, 126.1, 125.0, 124.5, 123.7, 120.2, 120.1, 52.2 (CO_2CH_3), 41.1 (*C*3/*C*3’), 40.9 (*C*3/*C*3’), 33.6 (*C*1’’/*C*1’’’), 33.6 (*C*1’’/*C*1’’’); ESI-MS: m/z calc. for $C_{44}H_{36}NaO_2^+$ 619.2608 found 619.2602 [M+Na$^+$].

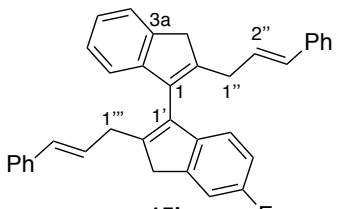
6.9.3. 2,2'-Dicinnamyl-6-methoxy-3*H*,3'*H*-1,1'-biindene (15g)



15g

Prepared according to the general procedure **F** using 2-cinnamyl-5-methoxy-1*H*-inden-3-yl trifluoromethanesulfonate (**23g**, 164 mg, 400 µmol, 1.0 eq), 2-cinnamyl-1*H*-inden-3-yl)trifluoroborane potassium salt (**25**, 149 mg, 440 µmol, 1.1 eq), Cs_2CO_3 (104 mg, 320 µmol, 0.8 eq), KF (55.8 mg, 960 µmol, 2.4 eq), PPh_3 (10.5 mg, 40.0 µmol, 0.1 eq) and (dppf)$PdCl_2$ (23.4 mg, 32.0 µmol, 8.0 mol%) in a mixture of THF/H_2O (30 mL, 9:1) with a reaction time of 21 h at 80 °C. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2 to 1:1) to yield the title compound **15g** as an orange oil (162 mg, 82%): R_f 0.32 (CH_2Cl_2/petrol ether, 1:2); ν_{max} (neat): 3024w, 2895w, 2832w, 1604m, 1477s, 1391w, 1283m, 1204m, 1075w, 1031m, 965s, 909m, 849w, 731s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (1H, d, ^3J 7.0, C4*H*), 7.33 (1H, d, ^3J 8.1, C4'*H*), 7.26–7.14 (12H, m), 7.10–7.07 (1H, m), 6.73 (1H, dd, ^3J 8.1, ^4J 2.5, C5'*H*), 6.62 (1H, d, ^4J 2.4, C7'*H*), 6.41–6.33 (2H, m, C3''*H*, C3'''*H*), 6.25–6.16 (2H, m, C2''*H*, C2'''*H*), 3.69 (3H, s, OC*H*$_3$), 3.59 (2H, d, ^3J 5.8, C3*H*), 3.52 (2H, d, ^4J 1.9, C2*H*), 3.34–3.27 (4H, m, C1''*H*, C1'''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.1 (*C*6'), 147.6 (*C*7a'), 146.5, 146.1, 145.0, 143.0, 137.5, 137.5, 135.0 (*C*3a'), 133.5, 133.5, 131.3, 131.3, 128.6, 128.6, 128.3, 128.2, 127.2, 127.2, 126.4, 126.2, 124.4, 124.0 (*C*4'), 123.6 (*C*4), 120.3, 110.4 (*C*5'), 105.9 (*C*'7), 55.6 (O*C*H$_3$), 41.0 (*C*3'), 40.3 (*C*3), 33.7 (*C*1''/*C*1'''), 33.6 (*C*1''/*C*1'''); ESI-MS: m/z calc. for $C_{37}H_{33}O^+$ 493.2526 found 493.2523 [M+H$^+$].

6.9.4. 2,2'-Dicinnamyl-5-fluoro-3*H*,3'*H*-1,1'-biindene (15h)

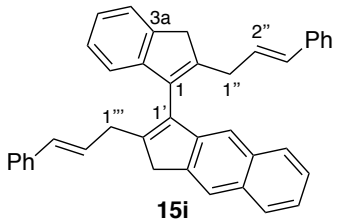


15h

Prepared according to the general procedure **F** using 2-cinnamyl-6-fluoro-1*H*-inden-3-yl trifluoromethanesulfonate (**23h**, 199 mg, 500 µmol, 1.0 eq), (2-cinnamyl-1*H*-inden-3-yl)trifluoro-

borane potassium salt (**25**, 186 mg, 550 μmol, 1.1 eq), Cs_2CO_3 (130 mg, 400 μmol, 0.8 eq), KF (69.7 mg, 1.20 mmol, 2.4 eq), PPh_3 (13.1 mg, 50.0 μmol, 0.1 eq) and (dppf)$PdCl_2$ (29.3 mg, 40.0 μmol, 8.0 mol%) in a mixture of THF/H_2O (15 mL, 9:1) with a reaction time of 21 h at 80 °C. The crude product was purified by column chromatography (petrol ether/toluene, 4:1) to yield the title compound **15h** as slightly yellow oil (104 mg, 43%): R_f 0.30 (*n*-pentane/toluene, 4:1); ν_{max} (neat): 2904w, 2362w, 1598m, 1493m, 1389m, 1154m, 1091m, 963m, 854m, 730s, 693s, 641m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 (1H, d, ^3J 7.0), 7.21–7.04 (13H, m), 7.00–6.95 (1H, m), 6.88 (1H, dd, ^3J 8.3, $^4J_{H\text{-}F}$ 5.3, C7'*H*), 6.84–6.79 (1H, m, C6'*H*), 6.34–6.27 (2H, m, C3''*H*/C3'''*H*), 6.17–6.08 (2H, m, C2''*H*/C2'''*H*), 3.57–3.43 (4H, m, C3*H*/C3'*H*), 3.27–3.18 (4H, m, C1''*H*/C1'''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.3 (d, $^1J_{C\text{-}F}$ 242, *C*5'), 146.0, 145.1, 144.8 (d, $^3J_{C\text{-}F}$ 8.5, *C*3a'), 144.4, 144.3, 142.9, 142.0 (d, $^4J_{C\text{-}F}$ 2.0, *C*7'a), 137.4, 133.4, 132.8, 131.4 (*C*3''/*C*3'''), 131.4 (*C*3''/*C*3'''), 128.6, 128.1 (*C*2''/*C*2'''), 128.1 (*C*2''/*C*2'''), 127.3, 126.4, 126.2, 126.1, 124.5, 123.7, 120.6 (d, $^3J_{C\text{-}F}$ 8.5, *C*7'), 120.1, 113.1 (d, $^2J_{C\text{-}F}$ 22.6, *C*6'), 111.4 (d, $^2J_{C\text{-}F}$ 23.2, *C*4'), 41.1 (*C*3), 41.0 (d, $^4J_{C\text{-}F}$ 2.3, *C*3'), 33.6 (*C*1''/*C*1'''), 33.6 (*C*1''/*C*1'''); ^{19}F NMR (471 MHz, $CDCl_3$): δ = –119.4 (1F, s); ESI-MS: m/z calc. for $C_{36}H_{30}F^+$ 481.2326 found 481.2327 [M+H$^+$].

6.9.5. 2-Cinnamyl-3-(2-cinnamyl-1*H*-inden-3-yl)-1*H*-cyclopenta[*b*]naphthalene (15i)

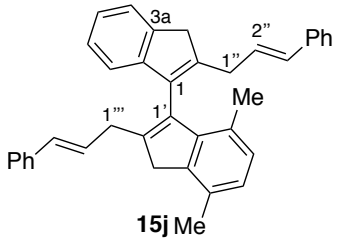


15i

Prepared according to the general procedure **F** using 2-cinnamyl-1*H*-cyclopenta[*b*]naphthalen-3-yl trifluoromethanesulfonate (**23i**, 172 mg, 400 μmol, 1.0 eq), (2-cinnamyl-1*H*-inden-3-yl)trifluoro-borane potassium salt (**25**, 149 mg, 440 μmol, 1.1 eq), Cs_2CO_3 (104 mg, 320 μmol, 0.8 eq), KF (55.8 mg, 960 μmol, 2.4 eq), PPh_3 (10.5 mg, 40.0 μmol, 0.1 eq) and (dppf)$PdCl_2$ (23.4 mg, 32.0 μmol, 8.0 mol%) in a mixture of THF/H_2O (30 mL, 9:1) with a reaction time of 21 h at 80 °C. The crude product was purified by column chromatography (*n*-pentane/toluene, 4:1 to 2:1) to yield the title compound **15i** as slightly brown oil (130 mg, 63%): R_f 0.34 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 2884w, 1721w, 1601w, 1449w, 1392w, 1156w, 1022w, 966m, 908m, 747s;^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.85 (1H, s), 7.84–7.81 (1H, m), 7.72–7.68 (1H, m), 7.51–7.48 (1H,

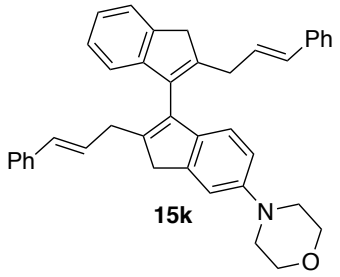
m), 7.44 (1H, s), 7.41–7.34 (2H, m), 7.27–7.14 (14H, m), 7.11–7.08 (1H, m), 6.44–6.35 (2H, m), 6.37–6.19 (2H, m), 3.78–3.57 (4H, m), 3.40–3.30 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.6, 146.2, 145.2, 145.1, 143.0, 141.0, 137.5, 133.6, 133.5, 133.2, 132.0, 131.6, 131.4, 128.6, 128.6, 128.2, 128.1, 127.9, 127.8, 127.3, 127.2, 126.5, 126.2, 126.2, 125.2, 124.8, 124.5, 123.7, 122.1, 120.3, 117.7, 41.1, 40.2, 33.9, 33.6; ESI-MS: m/z calc. for $C_{40}H_{33}^+$ 513.2568 found 513.2568 [M+H$^+$].

6.9.6. 2,2'-Dicinnamyl-4,7-dimethyl-3*H*,3'*H*-1,1'-biindene (15j)



Prepared according to the general procedure **F** using 2-cinnamyl-4,7-dimethyl-1*H*-inden-3-yl trifluoromethanesulfonate (**23j**, 408 mg, 1.00 mmol, 1.0 eq), (2-cinnamyl-1*H*-inden-3-yl)trifluoroborane potassium salt (**25**, 372 mg, 1.10 mmol, 1.1 eq), Cs_2CO_3 (261 mg, 800 µmol, 0.8 eq), KF (139 mg, 2.40 mmol, 2.4 eq), PPh_3 (26.2 mg, 100 µmol, 0.1 eq) and (dppf)$PdCl_2$ (58.5 mg, 80.0 µmol, 8.0 mol%) in a mixture of THF/H_2O (75 mL, 9:1) with a reaction time of 20 h at 80 °C. The crude product was purified by column chromatography (*n*-pentane/toluene, 4:1) to yield the title compound **15j** an orange oil (240 mg, 49%): R_f 0.41 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 3025w, 2919w, 1704w, 1599w, 1495m, 1458m, 1389w, 1306w, 1028w, 965m, 908m, 806w, 728s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50–7.43 (1H, m), 7.26–7.13 (12H, m), 7.05–7.03 (1H, m), 6.09 (2H, s), 6.37 (1H, d, *J* 10.8), 6.34 (1H, d, *J* 11.0), 6.25–6.13 (2H, m), 3.60–3.47 (2H, m), 3.47–3.37 (2H, m), 3.37–3.27 (2H, m), 3.27–3.18 (2H, m), 2.34 (3H, s), 2.00 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.3, 144.8, 143.6, 143.6, 142.5, 142.1, 137.6, 137.5, 136.4, 134.2, 131.3, 131.1, 130.2, 129.4, 128.6, 128.6, 127.9, 127.2, 127.2, 126.6, 126.1, 125.6, 124.4, 123.6, 120.1, 40.8, 39.8, 33.6, 33.3, 18.5, 18.3.

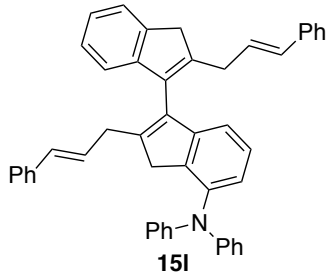
6.9.7. 4-(2,2'-Dicinnamyl-3*H*,3'*H*-[1,1'-biinden]-5-yl)morpholine (15k)



2-Cinnamyl-5-morpholino-2,3-dihydro-1*H*-inden-1-one (**17k**, 333 mg, 1.00 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (15 mL) and *i*-Pr_2NEt (198 µL, 1.20 mmol, 1.2 eq) and Tf_2O (207 µL, 1.25 mmol, 1.25 eq) were added. The black mixture was stirred at RT for 2.5 h before H_2O (20 mL) was added and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 20 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to yield the 2-cinnamyl-6-morpholino-1*H*-inden-3-yl trifluoromethanesulfonate as a colourless oil (**23k**, 334 mg, 718 µmol) which was used directly due to low stability.

According to the general procedure **F** using 2-cinnamyl-6-morpholino-1*H*-inden-3-yl trifluoromethanesulfonate (**23k**, 326 mg, 700 µmol, 1.0 eq), 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**, 276 mg, 770 µmol. 1.1 eq), Cs_2CO_3 (182 mg, 560 µmol, 0.8 eq), KF (97.6 mg, 1.68 mmol, 2.4 eq) and PPh_3 (18.4 mg, 70.0 µmol, 0.1 eq) and (dppf)$PdCl_2$ (41.0 mg, 56.0 µmol, 8.0 mol%) in a mixture of THF/H_2O (9.0 mL, 9:1) with a reaction time of 4 h at 80 °C. The crude product was purified by column chromatography (pure CH_2Cl_2 to CH_2Cl_2/Et_2O, 9:1) to yield the title compound **15k** as a yellow oil (380 mg, 69% over two steps): R_f 0.29 (CH_2Cl_2); ν_{max} (neat): 3024w, 2960m, 2889w, 1661w, 1449m, 1381w, 1304w, 1237m, 1121s, 960s, 879w, 811w, 695s; ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.40–7.35 (1H, m), 7.21–7.01 (13H, m), 6.98–6.94 (1H, m), 6.83 (1H, d, *J* 8.3), 6.67 (1H, dd, *J* 8.3, 2.3), 6.34–6.26 (2H, m), 6.20–6.11 (2H, m), 3.79–3.69 (4H, m), 3.52–3.42 (4H, m), 3.26–3.17 (4H, m), 3.07–2.99 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 149.8, 146.6, 145.1, 144.8, 143.5, 142.6, 139.3, 138.0, 137.9, 134.0, 133.3, 131.4, 131.2, 128.9, 128.8, 128.7, 127.4, 127.4, 126.5, 126.4, 126.4, 124.6, 123.9, 120.4, 120.3, 114.5, 112.9, 67.4, 50.9, 41.3, 41.2, 33.7; ESI-MS: m/z calc. for $C_{40}H_{38}NO^+$ 548.2948 found 548.2955 [$M+H^+$].

6.9.8. 2,2'-Dicinnamyl-*N*,*N*-diphenyl-3*H*,3'*H*-[1,1'-biinden]-4-amine (15l)

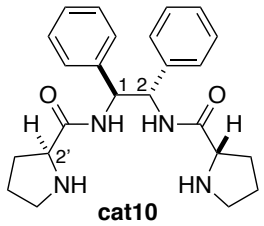


15l

Prepared according to the general procedure **F** using 2-cinnamyl-7-(diphenylamino)-1*H*-inden-3-yl trifluoromethanesulfonate (**23l**, 54.8 mg, 100 μmol, 1.0 eq), 2-(2-cinnamyl-1*H*-inden-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**, 39.4 mg, 110 μmol, 1.1 eq), Cs_2CO_3 (26.1 mg, 80.0 μmol, 0.8 eq), KF (13.9 mg, 240 mmol, 2.4 eq), PPh_3 (2.62 mg, 10.0 μmol, 0.1 eq) and $(dppf)PdCl_2$ (5.85 mg, 8.00 μmol, 8.0 mol%) in a mixture of THF/H_2O (2.0 mL, 9:1) with a reaction time of 16 h at 80 °C. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 9:1 to 4:1) to yield the title compound **15l** as a colourless oil (34.8 mg, 55%): R_f 0.54 (CH_2Cl_2/*n*-pentane, 4:1); ν_{max} (neat): 3025w, 2884w, 1586m, 1492s, 1277m, 1176w, 1076w, 1028w, 965m, 908m, 730s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 (1H, d, *J* 7.1), 7.26–7.12 (17H, m), 7.10–7.05 (5H, m), 6.99–6.92 (3H, m), 6.89 (1H, dd, *J* 7.5, 0.8), 6.39 (1H, d, *J* 15.8), 6.26–6.17 (2H, m), 6.06 (1H, dt, *J* 15.7, 6.9), 3.56 (2H, d, *J* 6.2), 3.32 (2H, d, *J* 6.7), 3.18 (2H, d, *J* 6.8), 3.05 (2H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.2, 147.6, 146.2, 145.1, 145.0, 142.9, 142.4, 138.2, 137.5, 137.5, 133.6, 133.1, 131.3, 131.2, 129.2, 128.6, 128.5, 128.3, 128.1, 128.0, 127.2, 127.1, 126.3, 126.1, 124.4, 123.7, 123.6, 122.9, 122.1, 120.4, 117.2, 41.1, 40.1, 33.6, 33.4; ESI-MS: m/z calc. for $C_{48}H_{39}NNa^+$ 652.2975 found 652.2964 [$M+Na^+$].

6.10. Catalyst Preparation

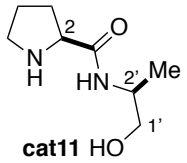
6.10.1. (2*S*,2'*S*)-*N*,*N*'-((1*S*,2*S*)-1,2-Diphenylethane-1,2-diyl)bis(pyrrolidine-2-carboxamide) (cat10)



cat10

Prepared according to a literature known procedure with small modifications:[110] Boc-L-proline (431 mg, 2.00 mmol, 2.0 eq) was dissolved in CH_2Cl_2 (10 mL), Et_3N (309 µL, 2.20 mmol, 1.1 eq) was added and the mixture was cooled to 0 °C before isobutyl chloroformate (260 µL, 2.00 mmol, 1.0 eq) was added. After 15 min at 0 °C, (1*S*,2*S*)-(–)-1,2-diphenyl-1,2-ethanediamine (212 mg, 1.00 mmol, 1.0 eq) was added and the mixture was warmed to RT. After 3.5 h, the reaction mixture was washed with aq. sat. NH_4Cl (10 mL), aq. sat. $NaHCO_3$ (15 mL) and brine (15 mL). Each aq. layer was reextracted with CH_2Cl_2 (20 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and TFA (1.0 mL) was added. The mixture was stirred at RT for 3 h before it was concentrated *in vacuo* and aq. NaOH (1.00 $mmol L^{-1}$, 15 mL) was added. The mixture was extracted with EtOAc (3x 15 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was recrystallized from MTBE (60 mL) to yield the title compound **cat10** as a white powder (407 mg, 40%, m.p. = 107–110 °C): R_f 0.05 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ +4.61 (*c* 1.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 8.54–8.38 (2H, m, CON*H*), 7.23–7.11 (6H, m), 7.10–6.97 (4H, m), 5.22–5.13 (2H, m, C1*H*, C2*H*), 3.75–3.66 (2H, m, C2'*H*), 3.00–2.91 (2H, m, C5'*H*), 2.89–2.80 (2H, m, C5'*H*), 2.20–2.00 (4H, m, C3'*H*, N*H*), 1.83–1.73 (2H, m, C3'*H*), 1.68–1.52 (4H, m, C4'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 175.3 (*C*ONH), 139.1, 128.5, 127.6, 127.5, 60.8 (*C*2'), 58.8 (*C*1, *C*2), 47.3 (*C*5'), 30.7 (*C*3'), 26.1 (*C*4'); Analytical data is in agreement with the literature.[110]

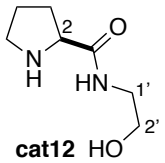
6.10.2. (*S*)-*N*-((*S*)-1-Hydroxypropan-2-yl)pyrrolidine-2-carboxamide (cat11)



cat11

Cbz-L-Proline (623 mg, 2.50 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (15 mL), Et_3N (351 µL, 2.50 mmol, 1.0 eq) was added and the mixture was cooled to 0 °C before isobutyl chloroformate (325 µL, 2.50 mmol, 1.0 eq) was added. After 15 min at 0 °C, L-alaninol (195 µL, 2.50 mmol, 1.0 eq) was added and the mixture was warmed to RT. After 3.5 h, the reaction mixture was washed with aq. sat. NH_4Cl (10 mL), aq. sat. $NaHCO_3$ (15 mL) and brine (15 mL). Each aq. layer was reextracted with CH_2Cl_2 (20 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and Pd/C (10 wt%, 133 mg, 125 µmol, 5.0 mol%) was added. The flask with the black suspension was evacuated and flushed with hydrogen gas. This cycle was repeated twice before the mixture was stirred under a hydrogen atmosphere at RT for 2 h. The reaction mixture was filtered through a plug of celite and the plug was rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo*. The crude product was recrystallized from *n*-hexane (50 mL) and EtOAc (1.0 mL) to yield the title compound **cat11** as a white powder (200 mg, 46%, m.p. = 93–95 °C): R_f 0.25 (EtOAc/MeOH, 2:1); $[\alpha]_D$ –82.2 (*c* 1.0 $CHCl_3$); ν_{max} (neat): 3295m, 2969m, 2938m, 2872m, 1645s, 1526s, 1452m, 1384m, 1256w, 1156w, 1101m, 1056m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.74 (1H, br s, CON*H*), 4.04–3.94 (1H, m, C2'*H*), 3.74 (1H, dd, ^3J 9.2, 5.4, C2*H*), 3.64 (1H, dd, ^1J 11.0, ^3J 3.5, C1'*H*), 3.52 (1H, dd, ^1J 11.0, ^3J 6.8, C1'*H*), 3.05–2.98 (1H, m, C4*H*, 2.92–2.87 (1H, m, C4*H*), 2.19–2.10 (1H, m, C3*H*), 1.93–1.85 (1H, m, C3*H*), 1.77–1.66 (2H, m, C5*H*), 1.67 (3H, d, ^3J 6.9, C3'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.4 (*C*ONH), 67.8 (*C*1'), 60.6 (*C*2), 47.9 (*C*2'), 47.4 (*C*4), 30.8 (*C*3), 26.3 (*C*5), 17.1 (*C*3'); ESI-MS: m/z calc. for $C_8H_{17}N_2O_2^+$ 173.1285 found 173.1287 [M+H$^+$].

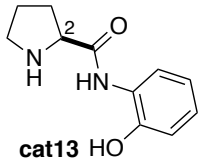
6.10.3. (*S*)-*N*-(2-Hydroxyethyl)pyrrolidine-2-carboxamide (cat12)



cat12

Cbz-L-Proline (4.99 g, 20.0 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (100 mL), Et_3N (2.81 mL, 20.0 mmol, 1.0 eq) was added and the mixture was cooled to 0 °C before isobutyl chloroformate (2.60 mL, 20.0 mmol, 1.0 eq) was added. After 20 min at 0 °C, ethanolamine (1.21 mL, 20.0 mmol, 1.0 eq) was added and the mixture was warmed to RT. After 5 h, the reaction mixture was washed with aq. sat. NH_4Cl (75 mL), aq. sat. $NaHCO_3$ (75 mL) and brine (75 mL). Each aq. layer was reextracted with CH_2Cl_2 (50 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by recrystallization from EtOH (10 mL). The solid was dissolved in MeOH (50 mL) and Pd/C (10 wt%, 1.06 g, 1.00 mmol, 5.0 mol%) was added. The flask with the black suspension was evacuated and flushed with hydrogen gas. This cycle was repeated four times before the mixture was stirred under a hydrogen atmosphere at RT for 17 h. The reaction mixture was filtered through a plug of celite and the plug was rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the title compound **cat12** was obtained as a colourless oil (2.50 g, 79%): R_f 0.13 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ –61.0 (*c* 1.0 MeOH); ν_{max} (neat): 3292m, 3090w, 2944m, 2873m, 1647s, 1532s, 1406m, 1253m, 1064m, 866w, 673w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (1H, br s, CON*H*), 3.69 (1H, dd, ^3J 9.1, 5.5, C2*H*), 3.63 (2H, t, ^3J 5.3, C2'*H*), 3.40–3.27 (2H, m, C1'*H*), 3.05–2.91 (3H, m, C5*H*, N*H*, O*H*), 2.89–2.83 (1H, m, C5*H*), 2.13–2.03 (1H, m, C3*H*), 1.87–1.78 (1H, m, C3*H*), 1.72–1.60 (2H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.7 (*C*ONH), 62.5 (*C*2'), 60.6 (*C*2), 47.3 (*C*5), 42.4 (*C*1'), 30.8 (*C*3), 26.3 (*C*4); ESI-MS: m/z calc. for $C_7H_{15}N_2O_2^+$ 159.1128 found 159.1130 [M+H$^+$].

6.10.4. (*S*)-*N*-(2-Hydroxyphenyl)pyrrolidine-2-carboxamide (cat13)



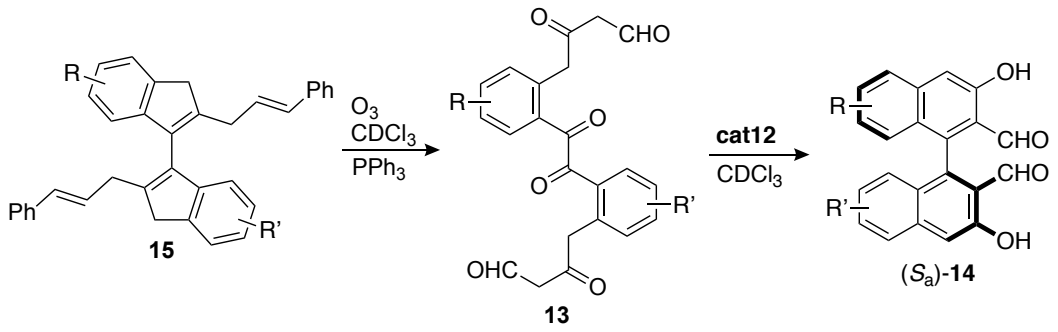
cat13

Prepared according to a literature known procedure with small modifications:[112] A mixture of Cbz-L-proline (2.99 g, 12.0 mmol, 1.0 eq) in THF (60 mL) and Et_3N (1.69 mL, 12.0 mmol, 1.0 eq) was cooled to 0 °C before ethyl chloroformate (1.14 mL, 12.0 mmol, 1.0 eq) was added dropwise.

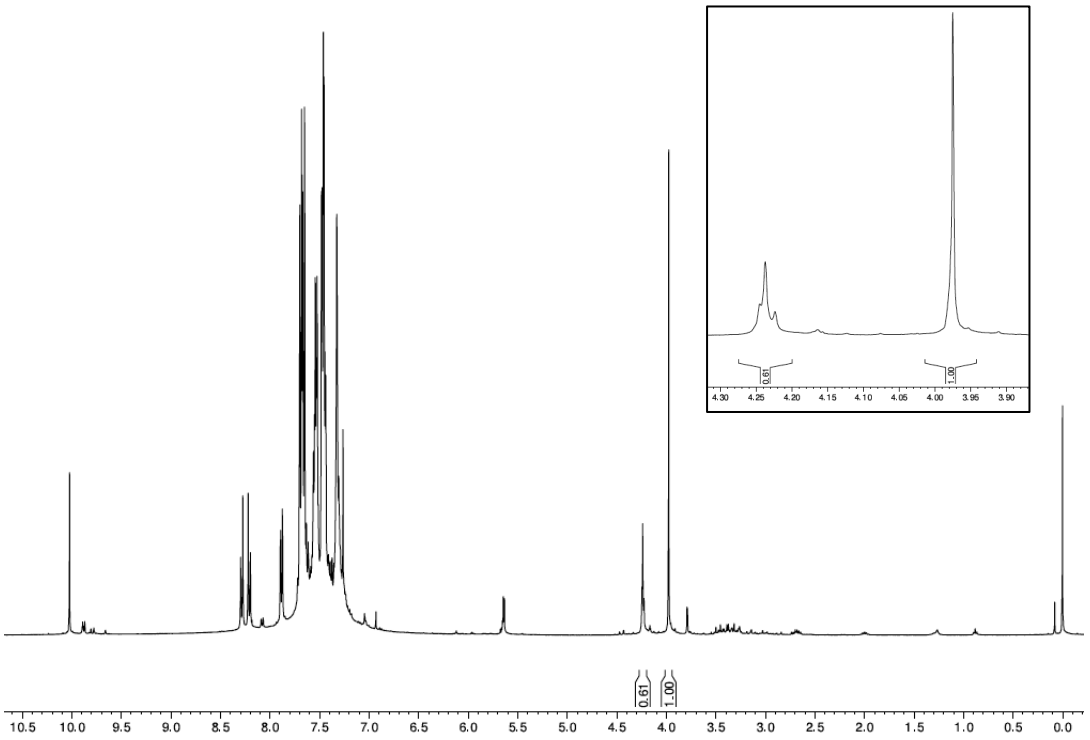
After stirring for 30 min at 0 °C, 2-aminophenol (1.31 g, 12.0 mmol, 1.0 eq) was added and the resulting mixture was stirred at 0 °C for 1 h before it was warmed to RT. After 3 h, aq. sat. $NaHCO_3$ (50 mL) and Et_2O (50 mL) were added, the org. layer was separated and washed with aq. HCl (1.00 $mmolL^{-1}$, 2x 50 mL). The org. layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (90 mL) and Pd/C (10 wt%, 639 mg, 600 μmol, 5.0 mol%) was added. The flask with the black suspension was evacuated and flushed with hydrogen gas. This cycle was repeated four times before the mixture was stirred under a hydrogen atmosphere for 15 h at RT. The reaction mixture was filtered through a plug of celite and the plug was rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the crude product was purified by recrystallization from EtOH (20 mL) to yield the title compound **cat13** as a grey solid (1.74 g, 70%, m.p. = 158 °C (decomp.)): R_f 0.13 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ –38.0 (*c* 1.0 CH_2Cl_2); ν_{max} (neat): 3353w, 3223w, 3063w, 2958w, 2870w, 2736w, 1637m, 1583m, 1526s, 1450s, 1379m, 1280s, 1102m, 921w, 832m, 754s, 619m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.12 (1H, br s, CON*H*), 8.19 (1H, d, ^3J 8.0), 6.89–6.83 (2H, m), 6.78–6.71 (1H, m), 3.72 (1H, dd, ^3J 9.2, 5.3, C2*H*), 3.00–2.93 (1H, m, C5*H*), 2.81–2.74 (1H, m, C5*H*), 2.09–1.99 (1H, m, C3*H*), 1.85–1.76 (1H, m, C3*H*), 1.67–1.58 (2H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.1 (*C*ONH), 146.2, 126.5, 123.3, 119.0, 118.7, 114.6, 60.9 (*C*2), 46.7 (*C*5), 30.3 (*C*3), 26.1 (*C*4); ESI-MS: m/z calc. for $C_{11}H_{15}N_2O_2^+$ 207.1128 found 207.1129 [$M+H^+$]. Analytical data is in agreement with the literature.[112]

6.11. Ozonolysis and Twofold 6-*(*enol*endo)-exo-trig* Cyclization

6.12. General Procedure G:



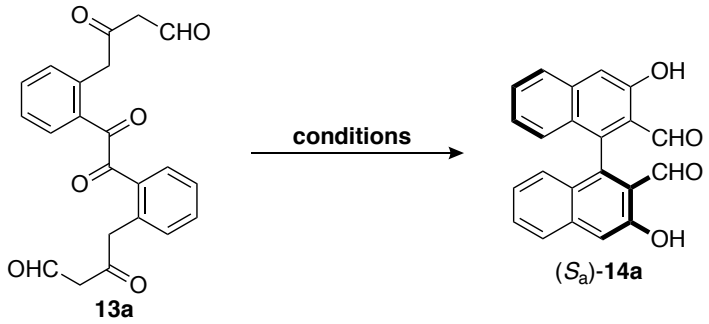
The specified biindene **15** (1.0 eq) dissolved in $CDCl_3$ (filtered through basic Al_2O_3) was added to a two-necked flask equipped with a glass stopper and a silicon septum with argon balloon and cooled to –50 °C. The stopper was replaced with a drying tube charged with $CaCl_2$ and the septum was replaced with an ozone inlet. An O_2/O_3 mixture (0.2 L/min, specified voltage) was bubbled through the solution until a slightly blue coloration was observed. The ozone inlet was replaced with the septum and argon was bubbled through the solution until the blue coloration disappeared. PPh_3 (4.4 eq) was added in one portion and the mixture was warmed to RT within 2–2:25 h. The slightly yellow mixture was filled into a volumetric flask containing a known amount of an internal standard (methyl benzoate, dimethyl terephthalate or methyl 4-nitrobenzoate) and was filled up with $CDCl_3$ to a known volume. The yield of the ozonolysis was determined from the ratio of the benzylic protons of the hexa-carbonyl substrates **13** compared to the signal of the methyl ester of the internal standard (methyl benzoate at 3.92 ppm, dimethyl terephthalate at 3.94 ppm or methyl 4-nitrobenzoate at 3.97 ppm). The signals of the benzylic protons the hexa-carbonyl substrates **13** have chemical shifts between 4.30–4.05 ppm. A specific amount of hexa-carbonyl substrate **13** (1.0 eq) in $CDCl_3$ (2.00 $mmolL^{-1}$, unless stated otherwise) was added to a round bottom flask containing the catalyst **cat12** and was stirred at RT for the specified time. The reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography.



Representative ^{1}H NMR spectra after the ozonolysis of 2,2'-dicinnamyl-3*H*,3'*H*-1,1'-biindene (**15a**) to determine the yield of hexa-carbonyl substrate **13a** by NMR.

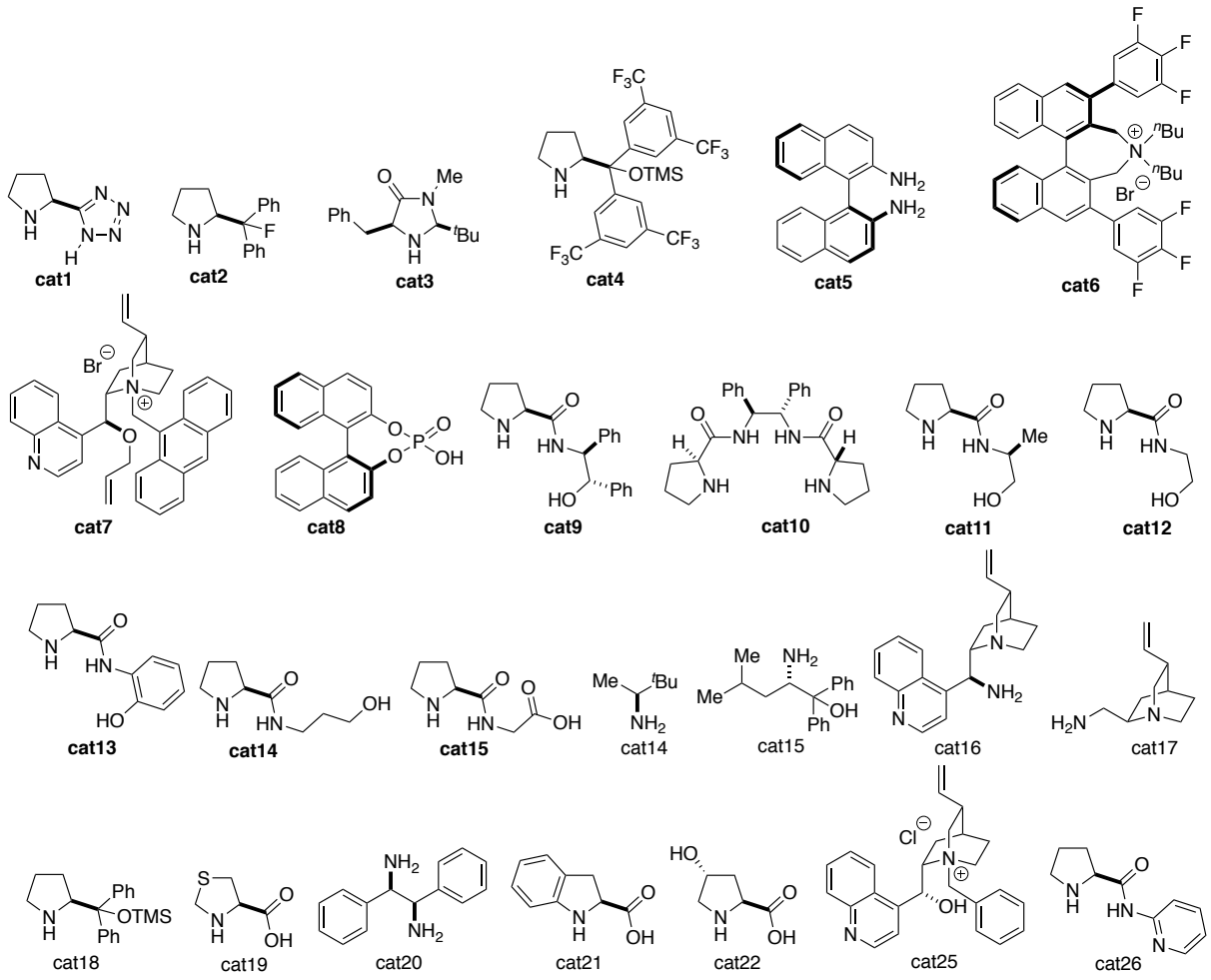
6.12.1. Examination of Catalysts and Conditions for the Twofold 6-*(*eno*lendo)-exo-trig* Cyclization

The reactions were performed with substrate **13a** according to the general procedure **G** using the catalysts which are listed on the next page.



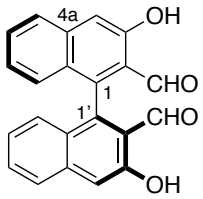
Entry[a]	Catalyst (mol%)	Time [h]	Solvent	Temperature [° C]	Additive	Yield [%]	e.r.
1	**cat1** (80)	48	$CDCl_3$	RT		65	67:33
2	**cat1** (40)	16	CH_2Cl_2/MeCN, 1:1	0		20	62:48
3	**cat1** (80)	39	CH_2Cl_2/MeCN, 1:1	–20		30	74:26
4	**cat1** (40)	17	CH_2Cl_2/fluorbenzene, 1:1	RT		61	55:45
5	**cat1** (40)	17	CH_2Cl_2/nitromethane, 1:1	RT		70	
6	**cat1** (40)	17	CH_2Cl_2/1,2-Dimethoxyethane, 1:1	RT		22	70:30
7	**cat1** (40)	17	CH_2Cl_2/EtOAc, 1:1	RT		56	62:38
8	L-Methionine (40)	36	CH_2Cl_2/DMF/H_2O, 2:1:1	RT		42	47:53
9	L-Isoleucine (40)	48	CH_2Cl_2/DMF/H_2O, 1.75:1:1	RT		42	54:46
10	L-Proline (40)	17	CH_2Cl_2/MeCN, 1:1	RT		26	51:49
11	L-Proline (80)	66	$CDCl_3$	RT		50	85:15
12	cat14 (40)	24	CH_2Cl_2/DMF/H_2O, 1.75:1:1	RT		-	-
13	cat15 (40)	24	CH_2Cl_2/DMF/H_2O, 1.75:1:1	RT		-	-
14	cat16 (40)	17	CH_2Cl_2/H_2O, 1:1	RT		40	56:44
15	cat17 (40)	17	CD_2Cl_2	RT		26	52:48
16	cat18 (40)	17	CD_2Cl_2	RT		-	-
17	**cat4** (40)	24	CD_2Cl_2	RT		traces	-
18	**cat5** (20)	113	$CDCl_3$	RT		11	68:32
19	cat19 (40)	17	CD_2Cl_2	RT		traces	-
20	**cat3** (40)	24	CD_2Cl_2	RT		-	-
21	cat20 (40)	24	CD_2Cl_2	RT		-	-
22	cat21 (40)	24	CD_2Cl_2	RT		-	-
23	cat22 (40)	20	$CDCl_3$	RT		traces	-
24	**cat2** (50)	16	$CDCl_3$	RT		9	-
25	**cat14** (80)	64	$CDCl_3$	RT		55	93:7
26	**cat15** (80)	22	$CDCl_3$	RT		72	91:9
27	**cat8** (40)	24	$CDCl_3$/Toluene-d_8, 1:0.2	RT		-	-
28	**cat6** (40)	19	$CDCl_3$/aq. KOH (1M), 5:1	RT		-	
29	**cat7** (40)	19	$CDCl_3$/aq. KOH (1M), 5:1	RT		-	
30	cat25 (40)	19	$CDCl_3$/aq. KOH (1M), 5:1	RT		-	
31	cat26 (50)	18	$CDCl_3$	RT		traces	-
32	**cat9** (80)	63	$CDCl_3$	RT		62	95:5
33	**cat9** (25)	18	MeCN-d_3	RT		12	-
34	**cat9** (25)	18	DMF-d_7	RT		-	-
35	**cat9** (25)	18	THF-d_8	RT		traces	
36	**cat9** (25)	18	Tolunene-d_8	RT		28	95:5
37	**cat10** (80)	63	$CDCl_3$	RT		74	95:5
38	**cat11** (80)	63	$CDCl_3$	RT		74	94:6
39	**cat12** (80)	48	$CDCl_3$	RT		65	96:4
40	**cat13** (80)	48	$CDCl_3$	RT		67	96:4
41	**cat12** (80)	41	$CDCl_3$	0	TfOH	13	-
42[b]	**cat12** (80)	24	$CDCl_3$	RT	TFA	76	92:8
43[b]	**cat12** (40)	44	$CDCl_3$	RT	TFA	63	87:13
44	**cat12** (80)	90	$CDCl_3$	RT	$NaHCO_3$	42	n.d.
45	**cat12** (80)	90	$CDCl_3$	RT	$KHCO_3$	28	n.d.
46	**cat12** (80)	90	$CDCl_3$	RT	Na_2CO_3	16	n.d.
47	**cat12** (80)	90	$CDCl_3$	RT	DABCO	63	64:36
48	**cat12** (80)	90	$CDCl_3$	RT	TMEDA	67	65:35
49[b]	**cat12** (80)	66	$CDCl_3$	RT		82	95:5
50[b]	**cat13** (80)	157	$CDCl_3$	RT		70	94:6

[a]10 μmol scale in 2.0 mmolL^{-1} of indicated solvent. [b]100 μmol scale

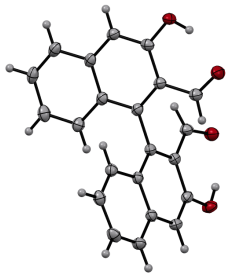


6.13. Scope of the Noncanonical Polyketide Cyclization

6.13.1. (S_a)-3,3'-Dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14a)



(S_a)-**14a**

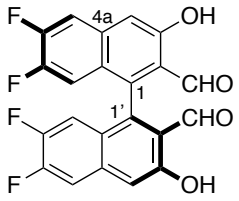


Reflection of (R_a)-**14a**

Prepared according to the general procedure **G** using 2,2'-dicinnamyl-3*H*,3'*H*-1,1'-biindene (**15a**, 1.04 g, 2.25 mmol, 1.0 eq), PPh_3 (2.60 g, 9.90 mmol, 4.4 eq) in $CDCl_3$ (90 mL) with a voltage = 2 for 30 min and then voltage = 4 for 30 min. In a 100 mL volumetric flask with 434 mg of methyl 4-nitrobenzoate a yield of 49% was determined for the hexa-carbonyl substrate **13a**. The aldol

condensation was performed using **13a** (1.00 mmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 127 mg, 800 µmol, 80 mol%) in $CDCl_3$ (100 mL) with a reaction time of 66 h at RT. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 2:1 to pure CH_2Cl_2) to yield the title compound **14a** as yellow solid (241 mg, 76%, e.r. = 96:4, 100 µmol scale: 82%, e.r. = 95:5, m.p. = 217–219 °C): R_f 0.51 (Et_2O/*n*-pentane, 1:9); $[\alpha]_D$ –127.3 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 3171w, 2877w, 1656s, 1558w, 1512w, 1410w, 1308, 1192w, 1149w, 877w, 751m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.02 (2H, s, O*H*), 9.53 (2H, d, ^5J 0.6, C*H*O), 7.80 (2H, d, ^3J 8.4, C5*H*), 7.55 (2H, ddd, ^3J 6.7, 6.6, ^4J 1.2, C6*H*), 7.51 (2H, s, C4*H*), 7.18 (2H, ddd, ^3J 6.8, 6.7, ^4J 1.2, C7*H*), 7.11–7.07 (2H, m, C8*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.9 (*C*HO), 156.6 (*C*2), 141.4 (*C*1), 138.2 (*C*4a), 130.8 (*C*6), 128.2 (*C*8a), 127.3 (*C*5/*C*8), 127.3 (*C*5/*C*8), 125.7 (*C*7), 121.4 (*C*3), 113.9 (*C*4); ESI-MS: m/z calc. for $C_{22}H_{14}O_4^-$ 341.0819 found 341.0815 [M–H$^+$]; The e.r of 96:4 of (S_a)-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14a**) was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a) t_R = 25.8 min and (R_a) t_R = 29.9 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst. Crystals suitable for X-ray crystallographic analysis were obtained by diffusion of *n*-pentane into a solution of (R_a)-**14a** (prepared with (*R*)-**14a**) in $CDCl_3$. A barrier of rotation $\Delta G^{\ddagger}_{433\,K}$ > 150 kJmol^{-1} was determined from the decrease in e.r. from 99:1 to 97.5 : 2.5 within 8 h in DMF at 160 °C (4 h e.r. 98.5 : 1.5). Further heating at 160 °C lead to decomposition of **14a** over 18 h.

6.13.2. (S_a)-6,6',7,7'-Tetrafluoro-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14b)

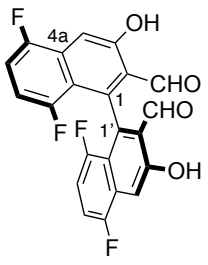


(S_a)-**14b**

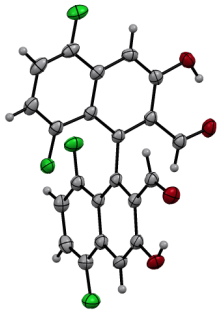
Prepared according to the general procedure **G** using 2,2'-dicinnamyl-5,5',6,6'-tetrafluoro- 3*H*,3'*H*-1,1'-biindene (**15b**, 107 mg, 200 µmol, 1.0 eq), PPh_3 (231 mg, 880 µmol, 4.4 eq) in $CDCl_3$ (20 mL) with a voltage = 2 for 10 min. In a 25 mL volumetric flask with 28.5 mg of methyl benzoate a yield of 59% was determined for the hexa-carbonyl substrate 1**3b**. The aldol condensation was performed using **13b** (50.0 µmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33

mg, 40 µmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 110 h at RT. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2 to 2:1 to pure CH_2Cl_2) to yield the title compound **14b** as yellow solid (12.8 mg, 61%, e.r. = 92:8, m.p. = 259–261 °C): R_f 0.50 (CH_2Cl_2); $[\alpha]_D$ –109.4 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 3152w, 2879w, 1660s, 1520m, 1395m, 1348w, 1286m, 1176m, 886w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.04 (2H, s, O*H*), 9.51 (2H, s, C*H*O), 7.59 (2H, dd, $^3J_{H\text{-}F}$ 10.9, ^3J 7.8, C5*H*), 7.51 (2H, s, C4*H*), 6.83 (2H, dd, $^3J_{H\text{-}F}$ 11.4, ^3J 8.0, C8*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.4 (*C*HO), 157.5 (d, $J_{C\text{-}F}$ 2.0, *C*2), 153.6 (dd, $^1J_{C\text{-}F}$ 258, $^2J_{C\text{-}F}$ 16.7, *C*6/*C*7), 151.0 (dd, $^1J_{C\text{-}F}$ 252, $^2J_{C\text{-}F}$ 16.4, *C*6/*C*7), 139.9 (dd, $^4J_{C\text{-}F}$ 6.6, $^5J_{C\text{-}F}$ 1.9, *C*1), 136.4 (d, $^3J_{C\text{-}F}$ 9.4, *C*4a), 124.9 (d, $^3J_{C\text{-}F}$ 6.6, *C*8a), 121.6 (d, $^5J_{C\text{-}F}$ 2.4, *C*3), 114.2 (dd, $^4J_{C\text{-}F}$ 5.5, $^5J_{C\text{-}F}$ 1.7, *C*4), 113.3 (dd, $^2J_{C\text{-}F}$ 18.5, $^3J_{C\text{-}F}$ 1.8, *C*5/*C*8), 113.3 (d, $^2J_{C\text{-}F}$ 18.8, *C*5/*C*8); ^{19}F NMR (471 MHz, CD_2Cl_2): δ = –127.7 (2F, m), –134.2 (2F, m); ESI-MS: m/z calc. for $C_{22}H_9F_4O_4^-$ 431.0442 found 413.0447 [M–H$^+$]. The e.r of 92:8 of (S_a)-6,6',7,7'-tetrafluoro-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14b**) was determined by HPLC using a *Chiralcel IA* analytical column (2.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 1:99): (S_a) t_R = 12.1 min and (R_a) t_R = 15.7 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst.

6.13.3. (S_a)-5,5',8,8'-Tetrafluoro-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14c)



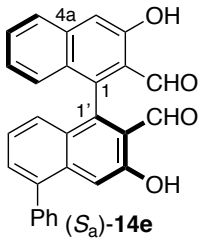
(S_a)-**14c**



Prepared according to the general procedure **G** using 2,2'-dicinnamyl-4,4',7,7'-tetrafluoro-3*H*,3'*H*-1,1'-biindene (**15c**, 160 mg, 300 µmol, 1.0 eq), PPh_3 (346 mg, 1.32 mmol, 4.4 eq) in $CDCl_3$ (10 mL) with a voltage = 2 for 25 min. In a 25 mL volumetric flask with 51.9 mg of dimethyl terephthalate a yield of 30% was determined for the hexa-carbonyl substrate **13c**. The aldol condensation was performed using **13c** (50.0 µmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33 mg, 40 µmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 76 h at RT. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:1) to

yield the title compound **14c** as yellow solid (4.9 mg, 24%, e.r. = 98:2, m.p. = 230–233 °C): R_f 0.57 (CH_2Cl_2); $[\alpha]_D$ –48.8 (*c* 0.2, benzene); ν_{max} (neat): 3110w, 2885w, 1662s, 1565w, 1521w, 1461w, 1381w, 1290m, 1204m, 732w; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ = 11.36 (2H, br s, O*H*), 10.16 (2H, s, C*H*O), 7.52 (2H, s, C4*H*), 7.40–7.33 (2H, m, C7*H*), 6.91–6.47 (2H, m, C6*H*); ^{13}C NMR (151 MHz, $(CD_3)_2SO$, ^{1}H cpd (waltz 16) and ^{19}F inverse gating (garp 4) decoupling) δ = 192.0 (*C*HO), 157.3 (*C*3), 155.9 (*C*8), 152.6 (C5), 138.2 (*C*1), 127.5 (*C*4a), 123.9 (*C*2), 117.8 (*C*8a), 112.3 (*C*7), 108.1 (*C*6), 103.3 (*C*4); ^{19}F NMR (565 MHz, $(CD_3)_2SO$): δ = –127.0 (2F, m, C5*F*), –113.4 (2F, m, C8*F*); ESI-MS: m/z calc. for $C_{22}H_9F_4O_4^-$ 431.0442 found 413.0446 [M–H$^+$]. The e.r of 98:2 of (S_a)-5,5',8,8'-tetrafluoro-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14c**) was determined by HPLC using a *Chiralcel IA* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 10:90): (S_a) t_R = 8.9 min and (R_a) t_R = 18.6 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst. Crystals suitable for X-ray crystallographic analysis were obtained by diffusion of *n*-pentane into a solution of (S_a)-**14c** in $CDCl_3$.

6.13.4. (S_a)-3,3'-Dihydroxy-5-phenyl-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14e)

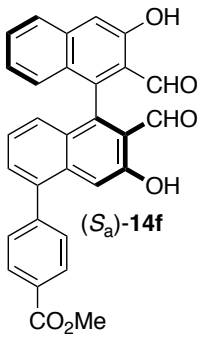


(S_a)-**14e**

Prepared according to the general procedure **G** using 2,2'-dicinnamyl-4-phenyl-3*H*,3'*H*-1,1'-biindene (**15e**, 108 mg, 200 μmol, 1.0 eq), PPh_3 (231 mg, 880 μmol, 4.4 eq) in $CDCl_3$ (20 mL) with a voltage = 2 for 10 min. In a 25 mL volumetric flask with 39.5 mg of methyl 4-nitrobenzoate a yield of 38% was determined for the hexa-carbonyl substrate **13e**. The aldol condensation was performed using **13e** (50.0 μmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33 mg, 40 μmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 74 h at RT. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:2) to yield the title compound **14e** as yellow oil (12.5 mg, 60%, e.r. = 91:9): R_f 0.43 (CH_2Cl_2); $[\alpha]_D$ –89.4 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 3157w, 3059w, 2878w, 1682s, 1514w, 1400w, 1274m, 1182w, 875w, 753m, 701w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.04 (1H, s, O*H*), 11.00 (1H, s, O*H*), 9.59 (1H, s, C*H*O),

9.53 (1H, s, C*H*O), 7.82 (1H, d, ^{3}J 8.4), 7.60–7.46 (9H, m), 7.27–7.19 (2H, m), 7.18–7.14 (1H, m), 7.14–7.10 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.6 (*C*HO), 196.6 (*C*HO), 156.6, 156.5, 141.7, 141.5, 139.7, 139.7, 138.2, 136.8, 131.4, 130.8, 130.0, 128.8, 128.6, 128.3, 128.0, 127.4, 127.3, 126.9, 125.7, 125.2, 121.5, 121.2, 113.9, 112.7; ESI-MS: m/z calc. for $C_{28}H_{19}O_4^+$ 419.1278 found 419.1267 [M+H$^+$]; The e.r of 91:9 of (S_a)-3,3'-dihydroxy-5-phenyl-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14e**) was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a) t_R = 25.7 min and (R_a) t_R = 36.6 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst.

6.13.5. Methyl (S_a)-4-(2,2'-diformyl-3,3'-dihydroxy-[1,1'-binaphthalen]-5-yl)-benzoate (14f)

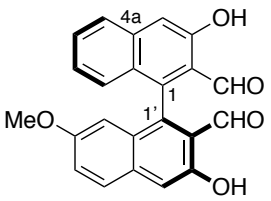


(S_a)-**14f**

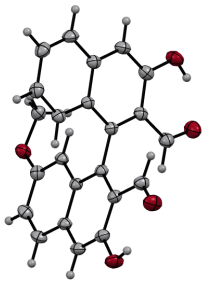
Performed according to the general procedure **G** using methyl 4-(2,2'-dicinnamyl-3*H* ,3'*H* -[1,1'-biinden]-4-yl)benzoate (**15f**, 89.5 mg, 150 μmol, 1.0 eq), PPh_3 (173 mg, 660 μmol, 4.4 eq) in $CDCl_3$ (25 mL) with a voltage = 2 for 5 min. In a 25 mL volumetric flask with anthracene (internal standard, 22.6 mg) a yield of 48% was determined for the hexa-carbonyl substrate **13f**. The aldol condensation was performed with **13f** (50.0 μmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33 mg, 40 μmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 72 h at RT. The crude product was purified column chromatography (CH_2Cl_2) to yield the title compound **14f** as a yellow oil (19.0 mg, 80%, e.r = 90:10, 98:2 on a 10 μmol scale): R_f 0.44 (CH_2Cl_2); $[\alpha]_D$ –207.2 (*c* 0.5, $CHCl_3$); ν_{max}(neat): 3160w, 2880w, 1721m, 1658s, 1515w, 1396w, 1279s, 1186w, 1118w, 1019w, 872w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.03 (1H, s, O*H*), 10.98 (1H, s, O*H*), 9.59 (1H, s, C*H*O), 9.54 (1H, s, C*H*O), 8.24–8.21 (2H, m, C2''*H* , C6''*H*), 7.83 (1H, d, *J* 8.4), 7.62–7.59 (2H, m, C3''*H*, C5''*H*), 7.59–7.55 (1H, m), 7.54 (1H, s), 7.52–7.48 (2H, m), 7.25–7.20 (2H, m), 7.17–7.13 (2H, m), 4.00 (3H, s, CO_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.5 (*C*HO), 196.5 (*C*HO), 167.0 (CO_2CH_3), 156.8, 156.6, 144.4, 141.6, 141.4, 138.6, 138.2,

136.3, 131.4, 130.9, 130.1, 130.1, 129.8, 128.6, 128.3, 127.5, 127.3, 127.3, 125.8, 125.1, 121.5, 121.3, 114.0, 112.3, 52.4 (CO_2CH_3); ESI-MS: m/z calc. for $C_{30}H_{20}O_6Na^+$ 499.1152 found 499.1158 [M+Na^+]; The e.r of 90:10 and 98:2 of methyl (S_a)-4-(2,2'-diformyl-3,3'-dihydroxy-[1,1'-binaphthalen]-5-yl)benzoate (**14f**) was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 20:80): (S_a) t_R = 27.7 min and (R_a) t_R = 35.9 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H* -tetrazole (**cat1**) as catalyst.

6.13.6. (S_a)-3,3'-Dihydroxy-7-methoxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14g)



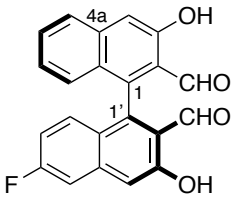
(S_a)-**14g**



Performed according to the general procedure **G** using 2,2'-dicinnamyl-6-methoxy-3*H*,3'*H*-1,1'-biindene (**15g**, 73.9 mg, 150 µmol, 1.0 eq), PPh_3 (173 mg, 660 µmol, 4.4 eq) in $CDCl_3$ (25 mL) with a voltage = 2 for 10 min and then with voltage = 4 for 5 min. In a 25 mL volumetric flask with 43.8 mg of methyl 4-nitrobenzoate a yield of 37% was determined for the hexa-carbonyl substrate **13g**. The aldol condensation was performed using **13g** (50.0 µmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33 mg, 40 µmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 44 h at RT. After 20 h, TFA (10% solution in $CDCl_3$, 29.6 µL, 40.0 µmol, 80 mol%) was added. The crude product was purified column chromatography (CH_2Cl_2/*n*-pentane, 2:1 to pure CH_2Cl_2) to yield the title compound **14g** as an orange solid (17.4 mg, 93%, e.r = 90:10, m.p. = 215–217 °C): R_f 0.32 (CH_2Cl_2); $[\alpha]_D$ –64.4 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 3176w, 3072w, 2877w, 1653s, 1559w, 1513m, 1392m, 1306m, 1261m, 1120m, 1029w, 873m, 752m, 699w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.04 (1H, s, O*H*), 10.93 (1H, s, O*H*), 9.55 (1H, d, ^5J 0.6, C*H*O), 9.48 (1H, d, ^5J, 0.6, C*H*O), 7.80 (1H, d, ^3J 8.5, C5*H*), 7.73 (1H, d, ^3J 9.0, C5'*H*), 7.56 (1H, ddd, ^3J 6.7, 6.7, ^4J 1.2, C6*H*), 7.51 (1H, s, C4*H*), 7.48 (1H, s, C4'*H*), 7.25 (1H, dd, ^3J 9.1, ^4J 2.6, C6'*H*), 7.21–7.17 (1H, m, C7*H*), 7.15–7.11 (1H, m, C8*H*), 6.27 (1H, d, ^4J 2.6, C8'*H*), 3.49 (3H, s, OC*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.8 (*C*HO), 196.6 (*C*HO), 157.3 (*C*7'), 156.5 (*C*2), 155.4 (*C*2'), 141.8 (*C*1), 138.9 (*C*1'), 138.3 (*C*4a), 134.1 (*C*4a'), 130.8 (*C*6), 129.0 (*C*8a'), 128.8 (*C*5'), 128.1 (*C*8a), 127.3 (*C*5/*C*8), 127.3 (*C*5/*C*8), 125.7 (*C*7), 124.2 (*C*6'), 121.5 (*C*3'), 121.2 (*C*3), 114.2

(*C*4'), 113.8 (*C*4), 104.8 (*C*8'), 55.4 (O*C*H$_3$); ESI-MS: m/z calc. for $C_{23}H_{17}O_5^+$ 373.1071 found 373.1067 [M+H$^+$]; The e.r of 90:10 of (S_a)-3,3'-dihydroxy-7-methoxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14g**) was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a) t_R = 30.8 min and (R_a) t_R = 36.0 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst. Crystals suitable for X-ray crystallographic analysis were obtained by diffusion of *n*-pentane into a solution of (R_a)-**14g** in $CDCl_3$.

6.13.7. (S_a)-6-Fluoro-3,3'-dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14h)



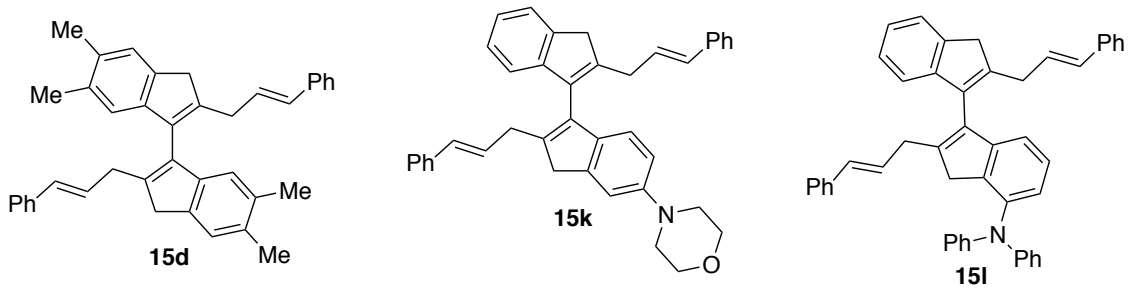
(S_a)-**14h**

Performed according to the general procedure **G** using 2,2'-dicinnamyl-5-fluoro-3*H*,3'*H*-1,1'-biindene (**15h**, 96.1 mg, 200 μmol, 1.0 eq), PPh_3 (231 mg, 880 μmol, 4.4 eq) in $CDCl_3$ (20 mL) with a voltage = 2 for 10 min. In a 25 mL volumetric flask with 27.8 mg of methyl 4-nitrobenzoate a yield of 53% was determined for the hexa-carbonyl substrate **13h**. The aldol condensation was performed using **13h** (50.0 μmol, 1.0 eq) and (*S*)-*N*-(2-hydroxyethyl)pyrrolidine-2-carboxamide (**cat12**, 6.33 mg, 40 μmol, 80 mol%) in $CDCl_3$ (25 mL) with a reaction time of 60 h at RT. After 48 h, TFA (10% solution in $CDCl_3$, 29.6 μL, 40.0 μmol, 80 mol%) was added. The crude product was purified column chromatography (CH_2Cl_2/petrol ether, 1:2) to yield the title compound **14h** as yellow solid (15.4 mg, 85%, e.r. = 94:6, m.p.= 260–262 °C): R_f 0.34 (CH_2Cl_2); $[\alpha]_D$ –96.5 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 3163w, 2879w, 1658s, 1560w, 1512w, 1389w, 1283m, 1183m, 1139w, 1048w, 980w, 880w, 753m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.12 (1H, s, O*H*), 11.00 (1H, s, O*H*), 9.54 (1H, d, ^5J 0.6, C*H*O), 9.50 (1H, d, ^5J 0.6, C*H*O), 7.81 (1H, d, ^3J 8.4, C5*H*), 7.56 (1H, ddd, ^3J 6.7, 6.7, ^4J 1.1, C6*H*), 7.53 (1H, s, C4*H*), 7.45 (1H, s, C4'*H*), 7.41 (1H, dd, $^3J_{H\text{-}F}$ 9.6, ^4J 2.6, C5'*H*), 7.22–7.18 (1H, m, C7*H*), 7.11 (dd, $^3J_{H\text{-}F}$ 9.6, ^3J 5.4, C8'*H*), 7.09–7.06 (1H, m, C8*H*), 6.98–6.93 (1H, m, C7'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 196.3 (*C*HO), 163.8 (d, $^1J_{C\text{-}F}$ 245, *C*6'), 157.5 (*C*2'), 156.6 (*C*2), 141.7 (*C*1'), 140.8 (*C*1), 139.8 (d, $^3J_{C\text{-}F}$ 11.0, *C*4a'), 138.2 (*C*4a), 130.9 (*C*8), 130.5 (d, $^3J_{C\text{-}F}$ 10.1, *C*8'), 128.1 (*C*8a), 127.4 (*C*5), 127.1 (*C*6), 125.9 (*C*7), 125.4 (*C*8'a), 121.3

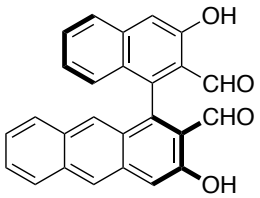
(*C*3), 120.9 (d, $^{5}J_{C\text{-}F}$ 2.3, *C*3'), 116.7 (d, $^{2}J_{C\text{-}F}$ 26.0, *C*7'), 114.1 (*C*4), 113.2 (d, $^{3}J_{C\text{-}F}$ 5.2, *C*4'), 110.4 (*C*5'); ^{19}F NMR (471 MHz, $CDCl_3$): δ = –106.6 (1F, s); ESI-MS: m/z calc. for $C_{22}H_{13}FO_4Na^+$ 383.0690 found 383.0687 [M+Na^+]; The e.r of 94:6 of (S_a)-6-fluoro-3,3'-dihydroxy-5-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14h**) was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a) t_R = 25.4 min and (R_a) t_R = 30.4 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst.

6.14. Limitations

The substrates from following precursors **15** could not be prepared by the fourfold ozonolysis due to competing oxidation processes.



6.14.1. (S_a)-1-(2-Formyl-3-hydroxynaphthalen-1-yl)-3-hydroxyanthracene-2-carbaldehyde (14i)

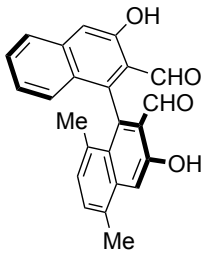


(S_a)-**14i**

The preparation of (S_a)-1-(2-formyl-3-hydroxynaphthalen-1-yl)-3-hydroxyanthracene-2-carbaldehyde (**14i**) was examined according to the the general procedure **G** using 2-cinnamyl-3-(2-cinnamyl-1*H*-inden-3-yl)-1*H*-cyclopenta[*b*]naphthalene (**15i**). Due the low yields in the ozonolysis step and only obtaining trace amounts of product from the aldol condensation step, further investigations were stopped. However, an e.r. 98:2 of the product **14i** was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a)-**14i**

t_R = 35.1 min and (R_a)-**14i** t_R = 41.4 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst.

6.14.2. (S_a)-3,3'-Dihydroxy-5,8-dimethyl-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (14j)

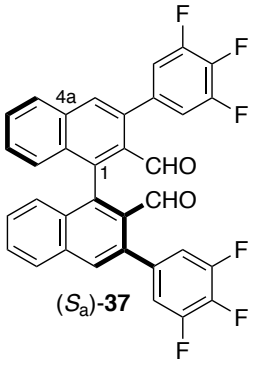


(S_a)-**14j**

The preparation of (S_a)-3,3'-dihydroxy-5,8-dimethyl-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14j**) was examined according to the the general procedure **G** using 2,2'-dicinnamyl-4,7-dimethyl-3*H*,3'*H*-1,1'-biindene (**15j**). Due to low yields in the ozonolysis step and only obtaining trace amounts of product from the aldol condensation step, further investigations were stopped. However, an e.r. of 82:18 of the product **14j** was determined by HPLC using a *Chiralcel IC-3* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 2:98): (S_a)-**14j** t_R = 19.7 min and (R_a)-**14j** t_R = 26.4 min; racemic reference material was obtained with *rac*-5-(2-pyrroidinyl)-1*H*-tetrazole (**cat1**) as catalyst.

6.15. Applications of the Noncanonical Polyketide Cyclization Products

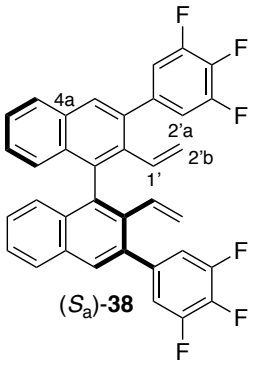
6.15.1. (S_a)-3,3'-Bis(3,4,5-trifluorophenyl)-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (37)



(S_a)-3,3'-Dihydroxy-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**14a**, 243 mg, 400 μmol, 1.0 eq, e.r. = 99.4:0.6 after one crystallization from a mixture of *n*-hexane/$CHCl_3$) was dissolved in CH_2Cl_2 (20 mL) and cooled to –78 °C. Triethylamine (169 μL, 1.20 mmol, 3.0 eq) was added, followed by the addition of Tf_2O (146 μL, 880 μmol, 2.2 eq). The cooling bath was removed and after 30 min the reaction mixture was washed with H_2O (2x 20 mL). The aq. layers were reextracted with CH_2Cl_2 (10 mL). The combined org. layers were washed with aq. HCl (1.00 $molL^{-1}$, 20 mL). The aq. layer was reextracted with CH_2Cl_2 (2x 10 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. 3,4,5-Trifluorobenzeneboronic acid (176 mg, 1.00 mmol, 2.5 eq) and $NaHCO_3$ (336 mg, 4.00 mmol, 10 eq) were added to the residue under an argon atmosphere. THF (9.0 mL) and H_2O (1.0 mL) were added followed by the addition of $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol, 5.0 mol%) and the suspension was stirred at RT for 18 h. H_2O (20 mL) was added and the mixture was extracted with Et_2O (2x 30 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2 to 1:1) to yield the title compound **37** as a slightly yellow solid (215 mg, 94% yield over two steps, e.r. = 98.3:1.7; after crystallization from *i*-PrOH: 84% yield over two steps, e.r. = >99:1, m.p. = 231 °C (decomp.)): R_f 0.33 (CH_2Cl_2/*n*-pentane, 1:1); $[\alpha]_D$ +13.1 (*c* 1.0, $CHCl_3$); ν_{max} (neat): 3067w, 2862w, 2752w, 1697s, 1616m, 1527s, 1437w, 1363w, 1241m, 1045m, 906w, 858w, 753w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.83 (2H, s, C*H*O), 8.00 (2H, d, ^3J 8.3, C5*H*), 7.97 (2H, s, C4*H*), 7.67–7.63 (2H, m, C6*H*), 7.41 (2H, m, C7*H*), 7.19–7.10 (6H,

m, C8*H*, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.4 (*C*HO), 151.0 (ddd, $^{1}J_{C\text{-}F}$ 251, $^{2}J_{C\text{-}F}$ 10.0, $^{3}J_{C\text{-}F}$ 4.3), 140.3 (*C*2), 139.7 (dt, $^{1}J_{C\text{-}F}$ 252, $^{2}J_{C\text{-}F}$ 15.2), 136.8 (*C*3), 135.8 (m), 134.6 (*C*4a), 132.7 (*C*8a), 131.2 (*C*4), 131.1 (*C*2), 129.8 (*C*6), 128.7 (*C*5), 128.5 (*C*7), 127.1 (*C*8), 114.2 (m); ESI-MS: m/z calc. for $C_{34}H_{17}F_6O_2^+$ 571.1127 found 571.1131 [M+H$^+$]; The e.r. of >99:1 of (S_a)-3,3'-bis(3,4,5-trifluorophenyl)-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**37**) was determined by HPLC using a *Chiralcel AD-H* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 10:90): (S_a) t_R = 7.63 min and (R_a) t_R = 10.63 min; racemic reference material was obtained by performing the reaction with *rac*-**14a**.

6.15.2. (S_a)-3,3'-Bis(3,4,5-trifluorophenyl)-2,2'-divinyl-1,1'-binaphthalene (38)

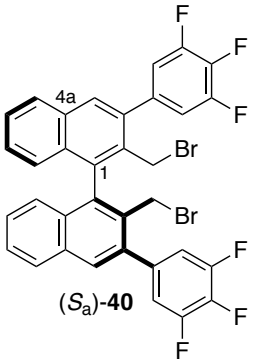


(S_a)-**38**

PPh_3MeI (80.8 mg, 200 μmol, 4.0 eq) was suspended in THF (1.0 mL), cooled to 0 °C and KO^{t}Bu (22.4 mg, 200 μmol, 4.0 eq) was added. After 5 min, a solution of (S_a)-3,3'-bis(3,4,5-trifluorophenyl)-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**37**, 28.5 mg, 50.0 μmol, 1.0 eq) in THF (2.0 mL) was added and a colour change from yellow to orange was observed. The suspension was stirred at RT for 18 h before it was filtered through a plug of celite. The plug was rinsed with EtOAc (5.0 mL). The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:2) to yield the title compound **38** as a colourless oil (20.0 mg, 71%, e.r. = >99:1): R_f 0.22 (CH_2Cl_2/*n*-pentane, 1:9); $[\alpha]_D$ –40.1 (*c* 1.0, $CHCl_3$); ν_{max} (neat): 3060w, 1614m, 1524s, 1427m, 1361m, 1239m, 1042s, 987m, 904m, 854m, 750s, 705m, 647w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.90 (2H, d, ^{3}J 8.20, C5*H*), 7.84 (2H, s, C4*H*), 7.50–7.45 (2H, m, C6*H*), 7.31–7.27 (2H, m, C7*H*), 7.15–7.08 (6H, m, C8*H*), 6.23 (2H, dd, ^{3}J 17.9, 11.6, C1'*H*), 4.90 (2H, dd, ^{3}J 11.6, ^{2}J 1.4, C2'*H*), 4.63 (2H, dd, ^{3}J 17.9, ^{2}J 1.3, C2'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 150.9 (ddd, $^{1}J_{C\text{-}F}$ 250, $^{2}J_{C\text{-}F}$ 10.1, $^{3}J_{C\text{-}F}$ 4.2), 139.2 (dt, $^{1}J_{C\text{-}F}$ 250, $^{2}J_{C\text{-}F}$ 15.5), 138.2 (m), 136.6, 136.1, 134.1, 134.0, 132.7 (*C*8a), 132.3 (*C*4a), 129.7 (*C*4), 128.2 (*C*5), 127.3 (*C*7), 126.8 (*C*6), 126.4 (*C*8), 121.2 (*C*2'), 114.5 (m); The e.r. of >99:1 of (S_a)-3,3'-bis(3,4,5-

trifluorophenyl)-2,2'-divinyl-1,1'-binaphthalene (**38**) was determined by HPLC using a *Chiralcel AD-H* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 1:99): (R_a) t_R = 4.01 min and (S_a) t_R = 4.41 min; racemic reference material was obtained by performing the reaction with *rac*-**37**.

6.15.3. (S_a)-2,2'-Bis(bromomethyl)-3,3'-bis(3,4,5-trifluorophenyl)-1,1'-binaphthalene (40)

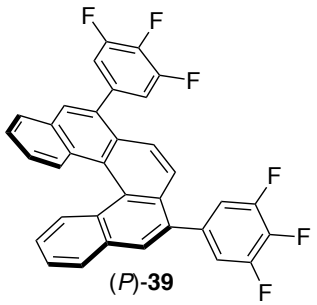


(S_a)-**40**

(S_a)-3,3'-Bis(3,4,5-trifluorophenyl)-[1,1'-binaphthalene]-2,2'-dicarbaldehyde (**37**, 57.0 mg, 100 µmol, 1.0 eq) was suspended in MeOH (4.0 mL), cooled to 0 °C and $NaBH_4$ (15.1 mg, 400 µmol, 4.0 eq) was added. After 30 min, H_2O (6.0 mL) was added and the suspension was extracted with CH_2Cl_2 (3x 10 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in THF (2.0 mL) and was cooled to 0 °C before PBr_3 (4.70 µL, 50.0 µmol, 0.5 eq) was added. After 2 h, the mixture was diluted with CH_2Cl_2, washed with H_2O (15 mL) and the org. layer was separated. The aq. layer was reextracted with CH_2Cl_2 (3x 4.0 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2) to yield the title compound **40** as a colourless oil (69.6 mg, 99%, e.r. = >99:1): R_f 0.12 (CH_2Cl_2/*n*-pentane, 1:9); $[\alpha]_D$ –46.9 (*c* 1.0, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.93 (2H, d, ^3J 8.1, C5*H*), 7.89 (2H, s, C4*H*), 7.57–7.54 (2H, m, C6*H*), 7.34 (2H, ddd, ^3J 6.9, 6.9, ^4J 1.2, C7*H*), 7.30–7.23 (4H, m, Ar*H*), 7.13 (2H, d, ^3J 8.6, C8*H*), 4.21–4.15 (4H, m, ArCH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.0 (ddd, $^1J_{C\text{-}F}$ 251, $^2J_{C\text{-}F}$ 9.9, $^4J_{C\text{-}F}$ 4.2), 139.7 (dt, $^1J_{C\text{-}F}$ 252, $^2J_{C\text{-}F}$ 15.2), 138.0 (*C*3), 136.5 (*C*1), 136.2 (m), 133.1 (*C*4a), 132.2 (*C*8a), 131.8 (*C*2), 130.8 (*C*4), 128.2 (*C*5), 128.0 (*C*6), 127.5 (*C*7), 127.3 (*C*8), 114.2 (m), 31.3 (Ar*C*H_2). The e.r. of >99:1 of (S_a)-2,2'-bis(bromomethyl)-3,3'-bis(3,4,5-trifluorophenyl)-1,1'-binaphthalene (**40**) was determined by HPLC using a *Chiralcel AD-H* analytical column (0.5 mLmin^{-1}, *i*-PrOH/*n*-heptane, 1:99): (R_a) t_R = 9.16 min and (S_a) t_R = 9.38 min;

racemic reference material was obtained by performing the reaction with *rac*-**37**. Analytical data is in agreement with literature.[44]

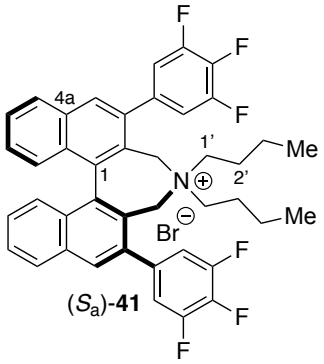
6.15.4. (*P*)-2,5-bis(3,4,5-trifluorophenyl)-[5]-helicene (39)



(*P*)-**39**

To a solution of LiHDMS (1.00 mmolL^{-1}, 1.00 mL, 1.00 mmol, 100 eq.) was added HMPA (176 µL, 1.00 mmol, 100 eq.) at 0 °C. (S_a)-2,2'-Bis-(bromomethyl)-3,3'-bis(3,4,5-trifluorophenyl)-1,1'-binaphthalene (**40**, 7.00 mg, 10.0 µmol, 1.0 eq) dissolved in THF (0.5 mL) was slowly added and the reaction mixture was stirred for 20 minutes at 0 °C. Aq. HCl (1.0 mmolL^{-1}, 10.0 mL) was added and the reaction mixture was stirred for 5 min at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3 x 5.0 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* (25 °C water bath). The residue was purified by column chromatography (pure *n*-pentane to CH_2Cl_2/*n*-pentane, 1:9) to yield the title compound **39** as white solid (3.6 mg, 67%, e.r. 98:2): R_f 0.20 (CH_2Cl_2/*n*-pentane, 1:9); $[\alpha]_D$ 914.6 (*c* 0.1, $CHCl_3$), ν_{max} (neat): 3066w, 2926w, 2854w, 1615m, 1528s, 1433m, 1360w, 1239m, 1044w, 787m, ^{1}H NMR (600 MHz, CD_2Cl_2) δ = 8.40 (2H, d, ^3J 8.8, C10*H*/C11*H*), 7.99–8.01(2H, m, C7*H*/C14*H*), 7.90 (2H, s, C1*H*/C6*H*), 7.75 (2H, s, C3*H*/C4*H*), 7.56–7.59 (2H, m, C8*H*/C13*H*), 7.26–7.32 (2H, m, C9*H*/C12*H*), 7.25–7.28 (4H, m, C2'*H*/C6'*H*); ^{13}C NMR-{^{1}H,^{19}F} (150 MHz, CD_2Cl_2) δ = 151.4 (*C*3'/*C*5'), 139.8 (*C*5'), 137.0 (*C*1'), 135.2 (*C*2), 132.0 (*C*6*a*/*C*14a), 131.3 (*C*10a/*C*10d), 130.4 (*C*2a/*C*4a), 129.3 (*C*10/*C*11), 128.9 (*C*1/*C*6), 128.5 (*C*7/*C*14), 128.2 (*C*10b/*C*10c), 127.4 (*C*8/*C*13), 125.7 (*C*9/*C*12), 125.0 (*C*3/*C*4), 115.0 (*C*2'/*C*6'); ^{19}F NMR (564 MHz, CD_2Cl_2): δ = –135.33 (4F, d, $^3J_{F\text{-}F}$ 20.4), –163.02 (2F, dd, $^3J_{F\text{-}F}$ 20.5, 20.4); The e.r. of 98:2 of (*P*)-2,5-bis(3,4,5-trifluorophenyl)-[5]-helicene (**39**) was determined by HPLC using a *Chiralcel AD-H* analytical column (1.0 mLmin^{-1}, *i*-PrOH/*n*-heptane, 1:99): (*P*) t_R = 11.82 min and (*M*) t_R = 5.47 min; racemic reference material was obtained by performing the reaction with *rac*-2,2'-bis-(bromomethyl)-3,3'-bis(3,4,5-trifluorophenyl)-1,1'-binaphthalene (**40**).

6.15.5. (S_a)-4,4-Dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (41)

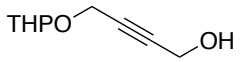


(S_a)-**41**

Performed according to a literature known procedure: [160] (S_a)-2,2'-Bis-(bromomethyl)-3,3'-bis(3,4,5-trifluorophenyl)-1,1'-binaphthalene (**40**, 42.0 mg, 60.0 µmol, 1.0 eq) was dissolved in MeCN (2.0 mL) and K_2CO_3 (12.4 mg, 90.0 µmol, 1.5 eq) and *n*-Bu_2NH (15.5 µL, 120 µmol, 2.0 eq) were added. The suspension was heated to reflux for 15 h. H_2O (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3x 5.0 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 19:1) to yield the title compound **41** as a white solid (37.1 mg, 83%, m.p. = 187–189 °C): R_f 0.10 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ +11.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.04–7.98 (4H, m, C4*H*, C5*H*), 7.64–7.59 (2H, m, C6*H*), 7.40–7.34 (2H, m, C7*H*), 7.33–7.18 (6H, m, C8*H*, Ar*H*), 5.02 (2H, d, ^2J 14.1, ArCH_2), 3.74 (2H, d, ^2J 14.0, ArCH_2), 3.32 (2H, t, *J* 13.0, C1'*H*), 2.68–2.57 (2H, m, C1'*H*), 1.20–0.94 (6H, m), 0.75 (6H, t ^3J 7.2, C4'*H*), 0.43–0.30 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 138.7 (*C*1), 137.2 (*C*3), 134.9 (m), 133.8 (*C*4a), 131.6 (*C*4), 131.2 (*C*8a), 128.8 (*C*5), 128.8 (*C*6), 128.2 (*C*7), 127.7 (*C*8), 123.4 (*C*2), 57.6 (Ar*C*H_2), 57.6 (*C*1'), 24.8, 19.5, 13.4 (*C*4'). The e.r. of >99:1 of (S_a)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (**41**) was determined by HPLC using a *Chiralcel OJ-RH* analytical column (1.0 mLmin^{-1}, H_2O/MeCN, 50:50): (R_a) t_R = 15.92 min and (S_a) t_R = 17.14 min; racemic reference material was obtained by performing the reaction with *rac*-**40**. Analytical data is in agreement with literature.[160]

6.16. Stereoselective Synthesis of Rotationally Restricted Sp^2-Sp^3 Atropisomers

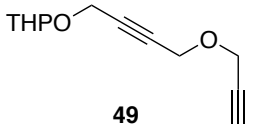
6.16.1. 4-((Tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-ol (60)



60

2-Butyne-1,4-diol (**50**, 8.61 mL, 120 mmol, 2.0 eq) and 3,4-dihydropyran (5.47 mL, 60.0 mmol, 1.0 eq) were suspended in CH_2Cl_2 (250 mL) and pyridinium *p*-toluenesulfonate (1.51 g, 6.00 mmol, 10 mol%) was added. The suspension was stirred at RT for 16 h before it was washed with H_2O (200 mL). The aq. layer was extracted with CH_2Cl_2 (100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the title compound **60** as a slightly yellow oil together with an unknown impurity (8.98 g, 88 %): R_f 0.41 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3428w, 2943m, 2869w, 1443w, 1346w, 1265w, 1129m, 1023s, 903w, 814w; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.82 (1H, t, *J* 3.5), 4.40–4.22 (4H, m), 3.89–3.79 (1H, m), 3.59–3.49 (1H, m), 2.30 (1H, br s), 1.92–1.40 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 97.0, 84.5, 81.8, 62.1, 54.4, 51.2, 30.3, 25.4, 19.1. The analytical data is in agreement with the literature.[161]

6.16.2. 2-((4-(Prop-2-yn-1-yloxy)but-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran (49)

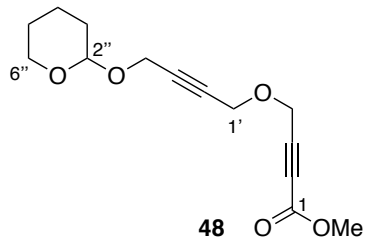


49

4-((Tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-ol (**60**, 8.17 g, 48.0 mmol, 1.0 eq) was dissolved in THF (200 mL), cooled to °C and NaH (60% in mineral oil, 1.72 g, 43.0 mmol, 0.9 eq) was added in portions over 10 min and the suspension was stirred at 0 °C for 15 min before propargyl bromide (80 wt% in toluene, 9.05 mL, 84.0 mmol, 1.75 eq) was added. The mixture was warmed to RT and stirred for 16 h. NaH (60% in mineral oil, 1.00 g, 25.0 mmol, 0.6 eq) and propargyl bromide (80 wt% in toluene, 1.00 mL, 9.28 mmol, 0.2 eq) were added and stirring at RT was continued for 5 h. H_2O (200 mL) and brine (50 mL) were added and the org. layer was separated. The aq. layer was extracted with Et_2O (2x 200 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to yield the title compound **49** was a colourless oil (6.28 g, 63%): R_f 0.15 (CH_2Cl_2); ν_{max} (neat):

3283w, 2945w, 2858w, 1443w, 1344w, 1264w, 1203w, 1119m, 1078s, 1023s, 971w, 903m, 814w, 669w; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.81 (1H, t, *J* 3.4), 4.39–4.28 (4H, m), 4.25 (2H, d, *J* 2.4), 3.88–3.80 (1H, m), 3.58–3.50 (1H, m), 2.45 (1H, t, *J* 2.4), 1.89–1.70 (2H, m), 1.67–1.49 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 97.0, 83.2, 81.1, 79.0, 75.1, 62.1, 56.9, 56.6, 54.3, 30.3, 25.4, 19.1. The analytical data is in agreement with the literature.[162]

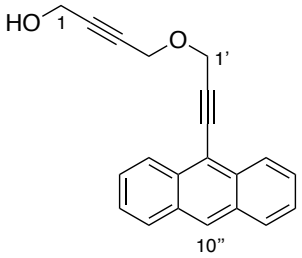
6.16.3. Methyl 4-((4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-yl)oxy)but-2-ynoate (48)



48

2-((4-(Prop-2-yn-1-yloxy)but-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran (**49**, 4.17 g, 20.0 mmol, 1.0 eq) was dissolved in THF (250 mL) and cooled to –78 °C before *n*-BuLi (1.55 $molL^{-1}$, 16.1 mL, 25.0 mmol, 1.3 eq) was added dropwise. The yellow mixture was stirred at –78 °C for 1 h followed by the dropwise addition of methyl chloroformate (2.32 mL, 30.0 mmol, 1.5 eq). After 1 h at –78 °C, the mixture was slowely warmed to RT. Water (100 mL), brine (50 mL) and Et_2O (100 mL) were added and the org. layer was separated. The aq. layer was extracted with Et_2O (100 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (pure CH_2Cl_2 to CH_2Cl_2/Et_2O, 9:1) to yield the title compound **48** as a slightly yellow oil (4.43 g, 83%): R_f 0.80 (CH_2Cl_2/Et_2O, 9:1); ν_{max} (neat): 2949w, 2239w, 1716s, 1436m, 1344w, 1250s, 1118m, 1057m, 1021s, 942m, 902m, 815w, 750m, 623w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.80 (1H, t, ^{3}J 3.4, C2''*H*), 4.39 (2H, s, C4*H*), 4.37–4.25 (4H, m, C1'*H*, C4'*H*), 3.87–3.80 (1H, m, C3''*H*), 3.79 (3H, s, OCH_3), 3.57–3.51 (1H, m, C3''*H*), 1.88–1.78 (1H, m, C4''*H*), 1.78–1.70 (1H, m, C5''*H*), 1.67–1.49 (4H, m, C4''*H*, C5''*H*, C6''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.6 (*C*1), 97.1 (*C*2''), 83.9 (*C*2'/*C*3'), 83.0 (*C*2/*C*3), 80.5 (*C*2'/*C*3'), 78.3 (*C*2/*C*3), 62.1 (*C*3''), 57.5 (*C*1'), 56.2 (*C*4), 54.3 (*C*4'), 53.0 (OCH_3), 30.3 (*C*5''), 25.4 (*C*6''), 19.1 (*C*4''); ESI-MS: m/z calc. for $C_{14}H_{18}O_5Na^+$ 289.1046 found 289.1047 [M+Na^+].

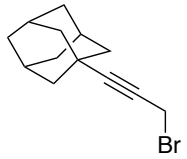
6.16.4. 4-((3-(Anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (47)



47

Magnesium turnings (1.17 g, 48.0 mmol, 3.0 eq) were suspended in THF (20 mL), a tenth of a solution of bis(2-bromophenyl)methane (**51**, 7.30 g, 22.4 mmol, 1.4 eq) in THF (140 mL) was added and the reaction was initiated with gentle heating with the heatgun. The remaining solution of bis(2-bromophenyl)methane was added dropwise and the resulting yellow suspension was stirred at RT for 16 h before methyl 4-((4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-yl)oxy)but-2-ynoate (**48**, 4.26 g, 16.0 mmol, 1.0 eq) in THF (40 mL) was added dropwise. The brown mixture was stirred at RT for 2 h and aq. HCl (1.00 molL^{-1}, 200 mL) was carefully added. The mixture was diluted with Et_2O (100 mL) and the org. layer was separated. The aq. layer was extracted with Et_2O (2x 100 mL) and the combined org. phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (100 mL) and *p*-TsOH·H_2O (50.0 mg, 263 μmol, 1.6 mol%) was added. The mixture was stirred at RT for 16 h before aq. sat. $NaHCO_3$ (100 mL), H_2O (100 mL) and CH_2Cl_2 (200 mL) were added. The org. layer was separated and the aq. layer was extracted with CH_2Cl_2 (2x 100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was recrystallized from a mixture of *n*-hexane (200 mL) and $CHCl_3$ (50 mL) yielding the title compound **47** as a yellow solid. The filtrate was concentrated *in vacuo* and purified by column chromatography (Et_2O/*n*-pentane, 2:3 to 1:1) to yield additional product **47** (combined 3.38 g, 70%, m.p. = 104–107 °C): R_f 0.33 (CH_2Cl_2/*n*-pentane, 1:1); ν_{max} (neat): 3350w, 3049w, 2915w, 2218w, 1624w, 1436w, 1381m, 1286w, 1128m, 1068s, 1009s, 991m, 841m, 781w, 726s; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.53 (2H, dd, ^3J 8.7, ^4J 0.9, C1''*H*, C8''*H*), 8.44 (1H, s, C10''*H*), 8.01 (2H, d, ^3J 8.4, C4''*H*, C5''*H*), 7.60–7.56 (2H, m, C2''*H*, C7''*H*), 7.53–7.48 (2H, m, C3''*H*, C6''*H*), 4.82 (2H, s, C1'*H*), 4.53 (2H, t, ^4J 1.8, C4*H*), 4.36 (2H, dt, ^3J 6.2, ^4J 1.8, C1*H*), 1.59 (1H, t, ^3J 6.2, O*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.0 (*C*9a''), 131.2 (*C*4a''), 128.8 (*C*4'', *C*5''), 128.3 (*C*10''), 126.9 (*C*2'', *C*7''), 126.7 (*C*1'', *C*8''), 125.8 (*C*3'', *C*6''), 116.5 (*C*9''), 95.5 (*C*3'/*C*2'), 85.5 (*C*3/*C*2), 83.8 (*C*3'/*C*2'), 81.4 (*C*3/*C*2), 58.1 (*C*1'), 57.2 (*C*4), 51.4 (*C*1); ESI-MS: m/z calc. for $C_{21}H_{16}O_2Na^+$ 323.1043 found 323.1041 [M+Na$^+$].

6.16.5. 1-(3-Bromoprop-1-yn-1-yl)adamantane

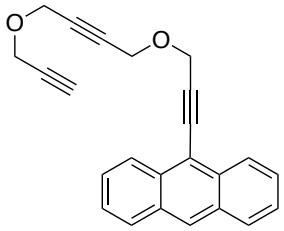


1-(2,2-Bibromovinyl)adamantane (**70**, 4.90 g, 15.3 mmol, 1.0 eq) in THF (50 mL) was cooled to –78 °C and *n*-BuLi (1.60 molL^{-1} hexanes, 21.0 mL, 33.7 mmol, 2.2 eq) was added over 10 min. After stirring at –78 °C for 45 min, a suspension of paraformaldehyde (2.30 g, 76.5 mmol, 5.0 eq) in THF (20 mL) was added and the reaction was warmed to RT. After 3 h, aq. sat. NH_4Cl (100 mL) and Et_2O (100 mL) were added. The org. layer was separated and the aq. layer was extracted with Et_2O (2x 100 mL). The combined org. layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 mL) and was cooled to 0 °C. PBr_3 (719 µL, 7.76 mmol, 0.5 eq) was added and the reaction was warmed to RT and stirred for 12 h. Aq. sat. NH_4Cl (100 mL) was added and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 100 mL). The combined org. layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol ether, 1:2) to yield the title compound as a colorless oil (3.24 g, 84%): R_f 0.66 (CH_2Cl_2/*n*-pentane, 1:9); ν_{max} (neat): 2907s, 2850m, 2360w, 2252w, 1450w, 1211w, 613w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.94 (2H, s), 1.99–1.92 (3H, m), 1.87–1.83 (6H, m), 1.72–1.65 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 96.1, 74.5, 42.6, 36.4, 29.9, 28.0, 16.1.

6.17. General Procedure H: Preparation of Trialkynes 46

4-((3-(Anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (**47**, 1.0 eq) was dissolved in THF (50 mmolL^{-1}), cooled to 0 °C and NaH (60 wt% in mineral oil, 3.0 eq) was added in portions over a period of 5 min. The specified propargyl bromide (2.0 eq) was added dropwise and the mixture was stirred at 0 °C for 10 min before it was warmed to RT and stirred for the specified time. The reaction mixture was diluted with aq. sat. NH_4Cl, H_2O and Et_2O and the org. layer was separated. The aq. layer was extracted with Et_2O (2x) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by column chromatography.

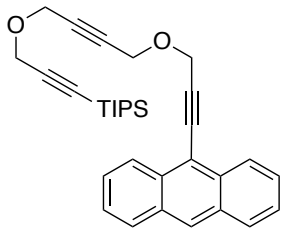
6.17.1. 9-(3-((4-(Prop-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-anthracene (46a)



46a

Prepared according to the general procedure **H** using 4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (**47**, 150 mg, 500 μmol, 1.0 eq), NaH (60 wt% in mineral oil, 60.0 mg, 1.50 mmol, 3.0 eq) and propargyl bromide (80 wt% in mineral oil, 108 μL, 1.00 mmol, 2.0 eq) in THF (10 mL) with a reaction time of 18 h at RT. After purification by column chromatography (Et_2O/*n*-pentane, 1:4) the title compound **46a** was obtained as an orange oil (145 mg, 86%): R_f 0.53 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3289w, 1668w, 1442m, 1352m, 1067s, 932m, 888m, 737s, 679m, 616m; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56–8.51 (2H, m), 8.44 (1H, s), 8.03–7.99 (2H, m), 7.61–7.56 (2H, m), 7.53–7.48 (2H, m), 4.83 (2H, s), 4.55 (2H, t, *J* 1.8), 4.37 (2H, t, *J* 1.8), 4.29 (2H, d, *J* 2.4), 2.46 (1H, t, *J* 2.4); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.0, 131.2, 128.8, 128.2, 126.9, 126.7, 125.8, 116.5, 95.5, 83.8, 82.6, 82.4, 79.0, 75.2, 58.0, 57.1, 57.0, 56.7; ESI-MS: m/z calc. for $C_{24}H_{18}NaO_2^+$ 361.1199 found 361.1201 [M+Na$^+$]; The product slowly decomposes in $CDCl_3$.

6.17.2. (3-((4-((3-(Anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)triisopropylsilane (46b)

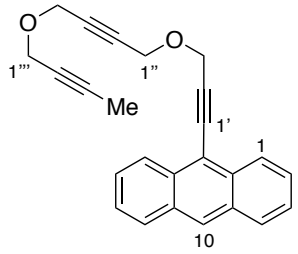


46b

9-(3-((4-(Prop-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (**47**, 102 mg, 300 μmol, 1.0 eq) in THF (5.0 mL) was cooled to –78 °C and *n*-BuLi (1.55 molL^{-1} in hexanes, 213 μL, 330 μmol, 1.2 eq) was added. After stirring at –78 °C for 1 h, chlorotriisopropylsilane (96.2 μL, 450 μmol, 1.5 eq) was added and the mixture was warmed to RT. H_2O (10 mL) was added and the

org. layer was separated. The aq. layer was extracted with Et_2O (2x 10 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2) to yield the title compound **46b** as an orange oil (64.7 mg, 44%): R_f 0.26 (CH_2Cl_2/*n*-pentane, 1:2); ν_{max} (neat): 2944m, 2865m, 1671w, 1598w, 1461m, 1346w, 1245w, 1074s, 999s, 884m, 739m, 678s; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (2H, dd, *J* 8.7, 0.2), 8.44 (1H, s), 8.01 (2H, d, *J* 8.5), 7.61–7.55 (2H, m), 7.53–7.47 (2H, m), 4.82 (2H, s), 4.55 (2H, t, *J* 1.8), 4.39 (2H, t, *J* 1.8), 4.33 (2H, s), 1.09–1.06 (21H, m); ESI-MS: m/z calc. for $C_{33}H_{38}O_2SiNa^+$ 517.2533 found 517.2529 [M+Na^+].

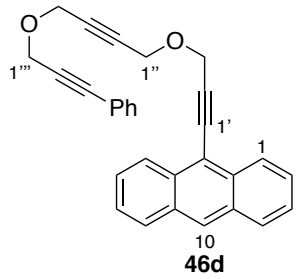
6.17.3. 9-(3-((4-(But-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (46c)



46c

Prepared according to the general procedure **H** using 4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (**47**, 601 mg, 2.00 mmol, 1.0 eq), NaH (60 wt% in mineral oil, 240 mg, 6.00 mmol, 3.0 eq) and 1-bromo-2-butyne (362 µL, 4.00 mmol, 2.0 eq) in THF (40 mL) with a reaction time of 3 h at RT. After purification by column chromatography (EtOAc/cyclohexane, 1:9) the title compound **46c** was obtained as an orange oil (566 mg, 80%): R_f 0.62 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3053w, 2852w, 1441w, 1353m, 1264w, 1116m, 1065s, 889m, 785m, 734s, 616m; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55–8.51 (2H, m, C1*H*, C8*H*), 8.44 (1H, s, C10*H*), 8.02–7.98 (2H, m, C4*H*, C5*H*), 7.61–7.55 (2H, m, C2*H*, C7*H*), 7.52–7.48 (2H, m, C3*H*, C6*H*), 4.82 (2H, s, C3'*H*), 4.53 (2H, t, ^4J 1.8, C1''*H*), 4.34 (2H, t, ^4J 1.8, C4''*H*), 4.24 (2H, q, ^4J 2.4, C1''*H*), 1.86 (3H, t, ^4J 2.4, C4''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.0 (*C*8a, *C*9a), 131.2 (*C*4a, *C*10a), 128.8 (*C*4, *C*5), 128.2 (*C*10), 126.9 (*C*2, *C*7), 126.7 (*C*1, *C*8), 125.8 (*C*3, *C*6), 116.5 (*C*9), 95.5 (*C*2'), 83.7 (*C*1'), 83.4 (*C*3'''), 82.8 (*C*3''), 82.2 (*C*2''), 74.4 (*C*2'''), 57.9 (*C*3'), 57.4 (*C*1'''), 57.1 (*C*1''), 56.8 (*C*4''), 3.8 (*C*4'''); ESI-MS: m/z calc. for $C_{25}H_{20}NaO_2^+$ 375.1356 found 375.1362 [M+Na^+]; The product slowly decomposes in $CDCl_3$.

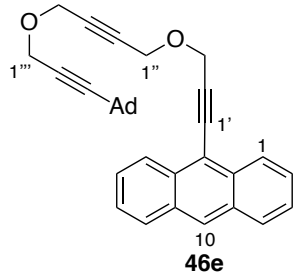
6.17.4. 9-(3-((4-((3-Phenylprop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (46d)



46d

Prepared according to the general procedure **H** using 4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (**47**, 150 mg, 500 μmol, 1.0 eq), NaH (60 wt% in mineral oil, 60.0 mg, 1.50 mmol, 3.0 eq) and (3-bromoprop-1-yn-1-yl)benzene (195 mg, 1.00 mmol, 2.0 eq) in THF (10 mL) with a reaction time of 64 h at RT. After purification by column chromatography (Et_2O/*n*-pentane, 1:4) the title compound **46d** was obtained as an orange oil (190 mg, 92%): R_f 0.57 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3054w, 2895w, 2850w, 1490w, 1442w, 1353m, 1259w, 1119m, 1069s, 889m, 757m, 692m, 617w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.55–8.51 (2H, m), 8.42 (1H, s), 8.01–7.97 (2H, m), 7.57 (2H, ddd, *J* 6.6, 6.5, 1.2), 7.51–7.46 (2H, m), 7.46–7.42 (2H, m), 7.33–7.27 (3H, m), 4.83 (2H, s), 4.56 (2H, t, *J* 1.8), 4.51 (2H, s), 4.42 (2H, t, *J* 1.8); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.0, 131.9, 131.2, 128.8, 128.7, 128.4, 128.2, 126.9, 126.7, 125.8, 122.5, 116.5, 95.5, 87.0, 84.3, 83.7, 82.6, 82.5, 58.0, 57.6, 57.1, 57.0; ESI-MS: m/z calc. for $C_{30}H_{22}O_2Na^+$ 437.1512 found 437.1505 [M+Na^+].

6.17.5. 1-(3-((4-((3-(Anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)-prop-1-yn-1-yl)adamantane (46e)

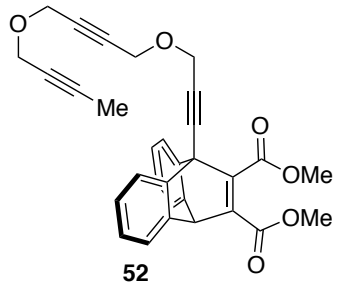


46e

Prepared according to the general procedure **H** using 4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-ol (**47**, 150 mg, 500 μmol, 1.0 eq), NaH (60 wt% in mineral oil, 60.0 mg, 1.50 mmol, 3.0 eq) and 1-(3-bromoprop-1-yn-1-yl)adamantane (190 mg, 750 μmol, 1.5 eq) in THF (10

mL) with a reaction time of 64 h at RT. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:2 to 2:1) the title compound **46e** was obtained as an orange oil (214 mg, 91%): R_f 0.74 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3053w, 2905s, 2851m, 2238w, 1451w, 1356m, 1070s, 1012w, 889w, 737m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.55–8.51 (2H, m), 8.43 (1H, s), 8.00 (2H, d, *J* 8.4), 7.58 (2H, ddd, *J* 6.5, 6.5, 1.2), 7.50 (2H, ddd, *J* 6.5, 6.5, 1.1), 4.82 (2H, s), 4.54 (2H, t, *J* 1.8), 4.33 (2H, t, *J* 1.8), 4.27 (2H, s), 1.97–1.91 (3H, m), 1.89–1.84 (6H, m), 1.71–1.63 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.0, 131.2, 128.8, 128.2, 126.9, 126.7, 125.8, 116.5, 96.1, 95.5, 83.7, 82.9, 82.0, 73.8, 57.9, 57.5, 57.1, 56.5, 42.9, 36.4, 29.7, 28.1; ESI-MS: m/z calc. for $C_{34}H_{32}O_2Na^+$ 495.2295 found 495.2292 [M+Na^+].

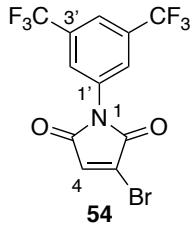
6.17.6. Dimethyl-9-(3-((4-(but-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (52)



52

9-(3-((4-(But-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (**46c**, 35.2 mg, 100 μmol, 1.0 eq) and dimethyl acetylenedicarboxylate (123 μL, 1.00 mmol, 10 eq) were heated neat to 140 °C for 15 min. After cooling to RT, the residue was purified by column chromatography (CH_2Cl_2/Et_2O, 98:2) to yield the title compound **52** as a slightly yellow oil (9.70 mg, 20%): R_f 0.80 (CH_2Cl_2/ Et_2O, 9:1); ν_{max} (neat): 2953w, 2854w, 2361m, 1721s, 1640w, 1458m, 1315m, 1266s, 1212m, 1121m, 1067s, 941w, 760m, 690w, 652w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70–7.62 (2H, m), 7.41–7.35 (2H, m), 7.13–7.03 (4H, m), 5.65 (1H, s), 4.63 (2H, s), 4.49 (2H, t, *J* 1.8), 4.32 (2H, t, *J* 1.8), 4.23 (2H, q, *J* 2.3), 3.84 (3H, s), 3.75 (3H, s), 1.86 (3H, t, *J* 2.3); ESI-MS: m/z calc. for $C_{31}H_{26}O_6Na^+$ 517.1622 found 517.1626 [M+Na^+].

6.17.7. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (54)



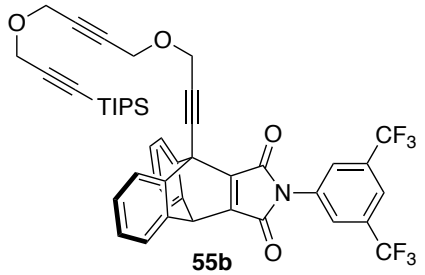
54

3,5-Bis(trifluoromethyl)aniline (2.29 g, 10.0 mmol, 1.0 eq) and bromomaleic anhydride (1.77 g, 10.0 mmol, 1.0 eq) were dissolved in glacial acetic acid (30 mL) and the solution was heated to 80 °C for 18 h. After cooled to RT, the mixture was concentrated *in vacuo*. The residual solid was recrystallized from *n*-hexane (40 mL) to yield the title compound **54** as a white solid (2.46 g, 63%, m.p. = 120–125 °C): R_f 0.48 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3074w, 1711s, 1592w, 1472m, 1407m, 1280s, 1118s, 1055s, 903m, 848m, 754m, 702m, 630m; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ = 8.17 (2H, s, C2'*H*, C6'*H*), 8.13 (1H, s, C4'*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.8 (*C*2/*C*5), 164.9 (*C*2/*C*5), 134.8 (*C*1'), 133.8 (*C*4), 132.8 (q, $^2J_{C\text{-}F}$ 33.8, *C*3'), 132.4 (*C*3), 127.6 (m, *C*2', *C*6'), 124.1 (q, $^1J_{C\text{-}F}$ 272, *C*F_3), 122.2 (m, *C*4'); ESI-MS: m/z calc. for $C_{13}H_8F_6NO_3Na^+$ 441.9484 found 441.9490 [M+CH_3OH+Na^+].

6.18. General Procedure I: Diels-Alder and Elimination

A specified anthracene **46** (1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 1.5 eq) were dissolved in *p*-xylene and heated 140 °C for the specified time. The mixture was concentrated *in vacuo* and the residue was dissolved in $CDCl_3$. Et_3N was added and the mixture was heated to 50 °C for the indicated time before the mixture was washed with aq. HCl (1.00 molL^{-1}). The aq. layer was extracted with CH_2Cl_2 (2x) and the combined org. layers were dried over Na_2SO_4 filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

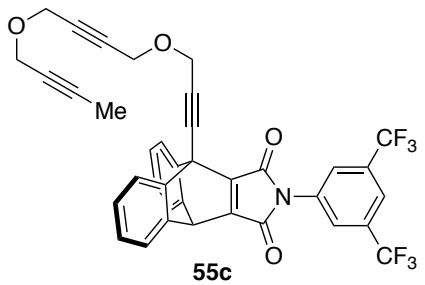
6.18.1. 13-(3,5-Bis(trifluoromethyl)phenyl)-9-(3-((4-((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione (55b)



55b

Prepared according to the general procedure **I** using (3-((4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)triisopropylsilane (**46b**, 59.4 mg, 120 μmol, 1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 69.9 mg, 180 μmol, 1.5 eq) in *p*-xylene (1.2 mL) with a reaction time of 20 min. The elimination was performed in $CDCl_3$ (3.0 mL) and Et_3N (150 μL) at 50 °C for 16 h. After purification by column chromatography (CH_2Cl_2/*n*-pentane, 1:2 to pure CH_2Cl_2) the title compound **55b** was obtained as orange oil (48.0 mg, 50%): R_f 0.15 (CH_2Cl_2/*n*-pentane, 1:2); ν_{max} (neat): 2945w, 2866w, 1728s, 1469m, 1390s, 1344w, 1278s, 1181m, 1136s, 1070s, 999w, 909w, 794w, 730m, 681m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.84–7.77 (5H, m), 7.46 (2H, dd, *J* 7.1, 1.2), 7.17 (2H, ddd, *J* 7.7, 7.5, 1.3), 7.12 (2H, ddd, *J* 7.5, 7.4, 1.2), 5.60 (1H, s), 4.74 (2H, s), 4.59 (2H, t, *J* 1.8), 4.37 (2H, t, *J* 1.7), 4.32 (2H, s), 1.10–1.05 (21H, m).

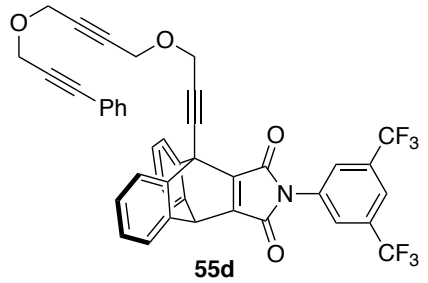
6.18.2. 13-(3,5-Bis(trifluoromethyl)phenyl)-9-(3-((4-(but-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione (55c)



55c

Prepared according to the general procedure **I** using 9-(3-((4-(but-2-yn-1-yloxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (**46c**, 70.5 mg, 200 μmol, 1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 116 mg, 300 μmol, 1.5 eq) in *p*-xylene (300 μL) with a reaction time of 30 min. The elimination was performed in $CDCl_3$ (3.0 mL) and Et_3N (100 μL) at 50 °C for 2.5 h. After purification by column chromatography (cyclohexane/EtOAc, 9:1) the title compound **55c** was obtained as a slightly yellow oil (115 mg, 87%): R_f 0.26 (cyclohexane/EtOAc, 9:1); ν_{max} (neat): 3069w, 2924w, 1729s, 1624w, 1470m, 1393s, 1279s, 1181m, 1136s, 1073m, 892w, 750w, 638w; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77–7.69 (5H, m), 7.39 (2H, dd, *J* 7.1, 1.3), 7.14–7.02 (4H, m), 5.52 (1H, s), 4.66 (2H, s), 4.51 (2H, t, *J* 1.7), 4.25 (2H, t, *J* 1.8), 4.14 (2H, q, *J* 2.4), 1.78 (3H, t, *J* 2.3); ESI-MS: m/z calc. for $C_{38}H_{28}F_6NO_5^+$ 692.1866 found 692.1857 [$M+H^+$].

6.18.3. 13-(3,5-Bis(trifluoromethyl)phenyl)-9-(3-((4-((3-phenylprop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-9,10-dihydro-9,10-[3,4]epipyrrolo-anthracene-12,14-dione (55d)

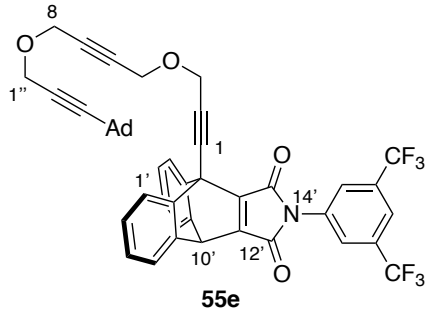


55d

Prepared according to the general procedure **I** using 9-(3-((4-((3-phenylprop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)anthracene (**46d**, 124 mg, 300 μmol, 1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 175 mg, 450 μmol, 1.5 eq) in *p*-xylene (1.2 mL) with a reaction time of 20 min. The elimination was performed in $CDCl_3$ (3.0 mL) and Et_3N (150 μL) at 50 °C for 16 h. After purification by column chromatography (Et_2O/*n*-pentane, 1:9) the title compound **55d** was obtained as orange oil (137 mg, 63%): R_f 0.38 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 3068w, 1728s, 1639w, 1470m, 1390s, 1345m, 1277s, 1179m, 1132s, 1068s, 891m, 794w, 756m, 694m, 637m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.84–7.77 (5H, m), 7.48–7.41 (4H, m), 7.34–7.26 (3H, m), 7.16 (2H, ddd, *J* 7.6, 7.5, 1.3), 7.11 (2H, ddd, *J* 7.5, 7.4, 1.2), 5.59 (1H, s), 4.75 (2H, s), 4.61 (2H, t, *J* 1.8), 4.49 (2H, s), 4.41 (2H, t, *J* 1.8); ^{13}C NMR (126

MHz, $CDCl_3$) δ = 163.7, 163.0, 156.5, 153.5, 143.5, 142.4, 133.4, 132.5 (q, $J_{C\text{-}F}$ 33.8), 131.9, 128.7, 128.4, 126.5, 126.1, 126.1, 124.7, 123.7, 122.9 (q, $J_{C\text{-}F}$ 273), 122.5, 121.1 (m), 87.8, 87.0, 84.3, 82.8, 82.3, 77.6, 57.6, 57.3, 57.1, 57.0, 49.8, 46.5; ESI-MS: m/z calc. for $C_{43}H_{30}F_6NO_5^+$ 754.2023 found 754.2012 [M+CH_3OH+H^+].

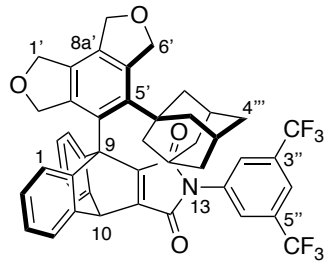
9-(3-((4-((3-(-Adamantan-1-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-9,10-dihydro-9,10-[3,4]epi-pyrroloanthracene-12,14-dione (55e)



55e

Prepared according to the general procedure **I** using 1-(3-((4-((3-(anthracen-9-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)adamantane (**46e**, 118 mg, 250 μmol, 1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 146 mg, 375 μmol, 1.5 eq) in *p*-xylene (0.7 mL) with a reaction time of 20 min. The elimination was performed in $CDCl_3$ (2.5 mL) and Et_3N (350 μL) at RT for 18 h. After purification by column chromatography (Et_2O/*n*-pentane, 1:4) the title compound **55e** was obtained as yellow oil (111 mg, 57%): R_f 0.50 (Et_2O/*n*-pentane, 1:4); ν_{max} (neat): 2906w, 2361w, 1728s, 1638w, 1470m, 1391s, 1277s, 1179m, 1134s, 1069s, 891m, 846w, 794w, 748m, 637m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83–7.77 (5H, m, C1*H*, C8*H*, Ar_F-*H*), 7.46 (2H, d, ^3J 7.1, C5*H*, C4*H*), 7.20–7.15 (2H, m, C2*H*, C7*H*), 7.15–7.10 (2H, m, C3*H*, C6*H*), 5.59 (1H, s, C10*H*), 4.74 (2H, s, C1'*H*), 4.58 (2H, s), 4.31 (2H, s), 4.25 (2H, s), 1.93 (3H, br s, C3''''*H*), 1.85 (6H, d, *J* 2.4, C2''''*H*), 1.67 (6H, s, C4''''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.7 (*C*12), 163.0 (*C*14), 156.5, 153.6, 143.5 (*C*8a, *C*9a), 142.4 (*C*4a, *C*10a), 133.4, 132.6 (q, $^2J_{C\text{-}F}$ 33.9, *C*CF_3), 126.5 (*C*3, *C*6), 126.2 (*C*2, *C*7), 124.7 (*C*4, *C*5), 123.7 (*C*1, *C*8), 122.9 (q, $^1J_{C\text{-}F}$ 273, C*C*F_3); 121.1 (m), 96.1, 87.8, 83.1, 81.9, 77.6, 73.8, 57.5, 57.3, 57.1 (*C*1'), 56.6, 49.8 (*C*9), 46.5 (*C*10), 42.9 (*C*2''''), 36.4 (*C*4''''), 29.7 (*C*1''''), 28.1 (*C*3''''); ESI-MS: m/z calc. for $C_{47}H_{39}F_6O_5Na^+$ 834.2625 found 834.2622 [M+CH_3OH+Na^+].

6.18.4. 9-(5-(Adamantan-1-yl)-1,3,6,8-tetrahydrobenzo[1,2-c:3,4-c']difuran-4-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-9,10-dihydro-9,10-[3,4]epipyrrolo-anthracene-12,14-dione (56e)

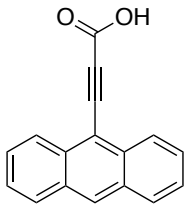


(–*ap*)-**56e**

$[Rh(COD)_2]BF_4$ (1.22 mg, 3.00 μmol, 20 mol%) and *rac*-BINAP (1.87 mg, 3.00 μmol, 20 mol%) were dissolved in CH_2Cl_2 and stirred under a dihydrogen atmosphere for 30 min before the mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (3.0 mL) and was added to a solution of 9-(3-((4-((3-(-adamantan-1-yl)prop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)prop-1-yn-1-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-9,10-dihydro-9,10-[3,4]epipyrro-loanthracene-12,14-dione (**55e**, 11.7 mg, 15.0 μmol, 1.0 eq). The mixture was stirred at RT for 1.5 days and was then heated to 40 °C for 24 h. The mixture was concentrated *in vacuo* and the crude products were purified by preparative TLC (Et_2O/*n*-pentane, 1:2) to yield two minor products (R_f = 0.67, 0.33 (Et_2O/*n*-pentane, 1:2)) and (*ap*)-**56e** as the major product: R_f = 0.28 (Et_2O/*n*-pentane, 1:2), ^{1}H NMR (600 MHz, $CDCl_3$, 253 K) δ = 7.83 (2H, s, C2''*H*, C6''*H*), 7.81 (1H, s, C4''*H*), 7.66 (1H, d, *J* 7.4, C4*H*), 7.42 (1H, dd, ^3J 7.2, ^4J 1.3, C5*H*), 7.40 (1H, d, ^3J 7.7, C1*H*), 7.39–7.36 (1H, m, C3*H*), 7.28–7.25 (1H, m, C2*H*), 7.11 (1H, d, ^3J 7.7, C8*H*), 6.97–6.93 (1H, m, C6*H*), 6.93–6.90 (1H, m, C7*H*), 5.82 (1H, d, ^2J 12.1, C6'*H*), 5.63 (1H, d, ^2J 11.6, C6'*H*), 5.56 (1H, s, C10*H*), 5.19–5.10 (2H, m, C8'*H*), 5.10–5.06 (1H, m, C1'*H*), 4.97 (1H, d, ^2J 12.2, C1'*H*), 2.01–1.91 (3H, m, C3'''*H*), 1.67–154 (6H, m, C2'''*H*), 1.54–1.36 (6H, m, C4'''*H*); ^{13}C NMR (150 MHz, $CDCl_3$, 253 K, extracted from HMBC) δ = 164.1 (*C*14), 160.7 (*C*12), 158.6 (*C*5'), 153.8 (*C*15), 150.8 (*C*4'), 147.8 (*C*10a), 147.0 (*C*8a), 142.8 (*C*3'a), 142.4 (*C*1), 139. 2 (*C*5'a), 138.4 (*C*4a), 133.1 (*C*8'a), 132.8 (*C*1''), 129.6 (*C*1'a), 127.7 (*C*3), 127.2 (*C*1), 126.9 (*C*8), 125.8 (*C*2), 125.6 (*C*2'', *C*6''), 125.2 (*C*5), 125.2 (*C*6), 124.8 (*C*7), 124.8 (*C*4), 122.7 (*C*F_3), 121.1 (*C*3'', *C*5''), 121.0 (*C*4''), 76.8 (*C*6'), 76.6 (*C*3'), 71.6 (*C*1'), 71.5 (*C*8'), 62.4 (*C*9), 47.4 (*C*10), 36 (br, *C*2'''), 36 (br, *C*4'''), 28 (br, *C*3'''); ^{1}H ^{1}H NOESY (600 MHz, $CDCl_3$, 253 K): C1*H*–C3'*H*, C1*H*–C2'''*H*, C1*H*–C3'''*H*, C8*H*–C3'*H*, C6'*H*–C2'''*H*,

C6'*H*–C3'''*H*, C6'*H*–C4'''*H*, C2''*H*–C2'''*H*, C2''*H*–C4'''*H*; ESI-MS: m/z calc. for $C_{46}H_{35}F_6NO_4Na^+$ 802.2362 found 802.2351 [M+Na^+].

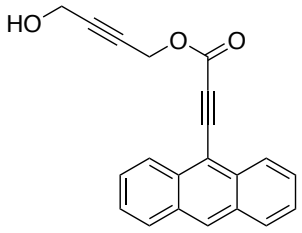
6.18.5. 3-(Anthracen-9-yl)propiolic acid (58)



58

9-(2,2-Dibromovinyl)anthracene (**57**, 1.81 g, 5.00 mmol, 1.0 eq) in CH_2Cl_2 (25 mL) was cooled to –78 °C and *n*-BuLi (1.58 $molL^{-1}$ in hexanes, 6.33 mL, 10.0 mmol, 2.0 eq) was added dropwise. The solution was stirred at –78 °C for 30 min before CO_2 (with a balloon) was bubbled through the solution for 30 min (caution: the needle gets blocked easily and needs to be changed occasionally). The suspension was warmed to RT and aq. HCl (1.00 $molL^{-1}$, 5.0 mL) added, followed by conc. HCl (10 mL). The precipitate was filtered off and washed with Et_2O (30 mL) to yield the title compound **58** as a yellow solid. The filtrate was extracted with Et_2O (20 mL) and the org. layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was recrystallized from EtOH to additionally yield **58** (combined 1.19 g, 97%, m.p. = 139–142 °C): ν_{max} (neat): 3362m, 3050m, 2939m, 2198s, 1653s, 1429m, 1357m, 1291m, 1246s, 1158m, 1087m, 1014m, 889m, 820m, 724s; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ = 8.86 (1H, s), 8.43 (2H, d, *J* 8.7), 8.21 (2H, d, *J* 8.5), 7.80–7.74 (2H, m), 7.67–7.61 (2H, m); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ = 154.4, 133.2, 131.1, 130.4, 129.2, 128.5, 126.3, 125.2, 111.9, 92.6, 81.0. The analytical data is in agreement with the literature.[163]

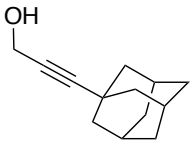
6.18.6. 4-Hydroxybut-2-yn-1-yl 3-(anthracen-9-yl)propiolate (61)



61

3-(Anthracen-9-yl)propiolic acid (**58**, 123 mg, 500 μmol, 1.0 eq), 4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-ol (**60**, 128 mg, 750 μmol, 1.5 eq) and PPh_3 (262 mg, 1.00 mmol, 2.0 eq) were dissolved in THF (15 mL) and cooled to 0 °C. A solution of DIAD (245 μL, 1.25 mmol, 2.5 eq) in THF (5.0 mL) was added dropwise. The mixture was warmed to RT over 30 min and then poured on H_2O (30 mL). The mixture was extracted with Et_2O (2x 30 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was suspended in MeOH (30 mL), *p*-TsOH·H_2O (19.0 mg, 100 μmol, 0.2 eq) was added and the mixture was stirred at RT for 1.5 h. Aq. sat. $NaHCO_3$ (10 mL) and H2O (30 mL) were added and the mixture was extracted with CH_2Cl_2 (3x 20 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 2:1) to yield the title compound **61** as a slightly yellow oil together with an inseparable impurity (96 mg): R_f 0.51 (Et_2O/*n*-pentane, 2:1); ν_{max} (neat): 3387w, 3054w, 2200m, 1708s, 1521w, 1442w, 1374w, 1220s, 1157m, 1081m, 1019m, 955w, 895w, 848w, 738m, 616w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.54–8.49 (3H, m), 8.00 (2H, d, *J* 8.3), 7.66–7.60 (2H, m), 7.55–7.49 (2H, m), 4.98 (2H, t, *J* 1.8), 4.37 (2H, t, *J* 1.7), 1.95 (1H, s), 1.26 (impurity); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.7, 134.4, 131.4, 131.0, 129.0, 128.1, 126.2, 126.2, 112.6, 90.8, 86.0, 85.2, 79.3, 53.7, 51.2, 22.0 (impurity).

6.18.7. 3-((Adamantan-1-yl)prop-2-yn-1-ol (69)

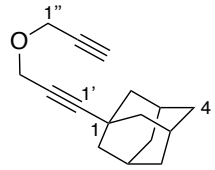


69

1-(2,2-Bibromovinyl)adamantane (**70**, 13.0 g, 40.6 mmol, 1.0 eq) in THF (150 mL) was cooled to –78 °C and *n*-BuLi (1.60 molL^{-1} in hexanes, 55.7 mL, 89.1 mmol, 2.2 eq) was added via a dropping

funnel over 15 min. The mixture turned bright yellow. After stirring 30 min at –78 °C, paraformaldehyde (6.08 g, 203 mmol, 5.0 eq) suspended in THF (50 mL) was added and the mixture was warmed to RT. After stirring 16 h at RT, H_2O (200 mL) and Et_2O (100 mL) were added and the org. layer was separated. The aq. layer was extracted with Et_2O (2x 100 mL) and the combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 1:4) to yield the title compound **69** as a colorless oil (6.44 g, 84%): R_f 0.36 (CH_2Cl_2); ν_{max} (neat): 3272m, 2903s, 2361w, 1452m, 1361w, 1186w, 1233m, 1100w, 996m, 733w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.26 (2H, s), 1.98–1.92 (3H, m), 1.88–1.84 (6H, m), 1.70–1.66 (6H, m), 1.61 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 94.7, 77.3, 51.6, 42.9, 36.5, 29.6, 28.1. The analytical data is in agreement with the literature.[143]

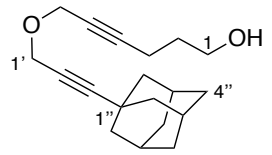
6.18.8. 1-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)adamantane (68)



68

3-((Adamantan-1-yl)prop-2-yn-1-ol (**69**, 6.28 g, 33.0 mmol, 1.0 eq) in THF (200 mL) was cooled to 0 °C and NaH (60 wt% in mineral oil, 3.96 g, 99.0 mmol, 3.0 eq) was added in four portions over 20 min. After stirring 30 min at 0 °C, propargyl bromide (80 wt% in mineral oil, 7.11 mL, 66.0 mmol, 2.0 eq) was added and the mixture was warmed to RT and stirred for 4 h. After cooling to 0 °C, H_2O (200 mL) and aq. sat. NH_4Cl (50 mL) were added and the mixture was diluted with Et_2O (200 mL). The org. layer was separated and the aq. layer was extracted with Et_2O (2x 150 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/*n*-pentane, 1:2) to yield the title compound **68** as a slightly yellow oil (6.23 g, 83%): R_f 0.50 (CH_2Cl_2/*n*-pentane, 1:2); ν_{max} (neat): 3292w, 2905s, 2852m, 1452m, 1359w, 1185w, 1082s, 931w, 666w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.25 (2H, s, C3'*H*), 4.23 (2H,d, *J* 2.4, C1''*H*), 2.43 (1H, t, *J* 2.4, C3''*H*), 1.98–1.92 (3H, m, C3*H*), 1.89–1.85 (6H, m, C2*H*), 1.71–1.66 (6H, m, C4*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 96.1 (*C*1'), 79.4 (*C*2''), 74.7 (*C*3''), 73.7 (*C*2'), 57.4 (*C*3'), 56.2 (*C*1''), 42.9 (*C*2), 36.5 (*C*4), 29.7 (*C*1), 28.1 (*C*3); ESI-MS: m/z calc. for $C_{16}H_{20}ONa^+$ 251.1406 found 251.1404 [M+Na^+].

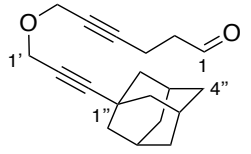
6.18.9. 6-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)hex-4-yn-1-ol (67)



67

1-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)adamantane (**68**, 4.57 g, 20.0 mmol, 1.0 eq) in THF (200 mL) was cooled to –78 °C and *n*-BuLi (1.60 molL^{-1} in hexanes, 15.0 mL, 24.0 mmol, 1.2 eq) was added dropwise. The mixture was stirred at –78 °C for 1 h before trimethylene oxide (1.57 mL, 24.0 mmol, 1.2 eq) and $BF_3{\cdot}Et_2O$ (2.96 mL, 24.0 mmol, 1.2 eq) were added. The mixture was warmed to RT and stirred for 16 h before H_2O (200 mL), aq. sat. $NaHCO_3$ (50 mL) and Et_2O (100 mL) were added. The org. layer was separated and the aq. layer extracted with Et_2O (2x 100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/petrol ether, 1:1) to yield the title compound **67** as a colourless oil (4.66 g , 81%): R_f 0.40 (Et_2O/*n*-pentane, 1:1); ν_{max} (neat): 3359w, 2904s, 2680w, 2361w, 2238w, 1718w, 1451m, 1347m, 1246w, 1184w, 1132w, 1071s, 927m; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.21 (2H, s, C1'*H*), 4.20 (2H, t, ^5J 2.2, C6*H*), 3.76 (2H, dt, ^3J 5.5, 6.0, C1*H*), 2.36 (2H, tt, ^3J 6.9, ^4J 2.2, C3*H*), 1.98–1.92 (3H, m, C3''*H*), 1.87–1.84 (6H, m, C2''*H*), 1.81–1.74 (2H, m, C2*H*), 1.70–1.66 (6H, m, C4''*H*), 1.49 (1H, t, ^3J 5.3, O*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 95.8 (*C*3'), 86.5 (*C*4), 76.2 (*C*5), 74.0 (*C*2'), 61.8 (*C*1), 57.3 (*C*1'), 56.9 (*C*6), 42.9 (*C*2''), 36.5 (*C*4''), 31.3 (*C*2), 29.7 (*C*1''), 28.1 (*C*3''), 15.5 (*C*3); ESI-MS: m/z calc. for $C_{19}H_{26}O_2Na^+$ 309.1825 found 309.1826 [M+Na$^+$].

6.18.10. 6-((3-(-Adamantan-1-yl)prop-2-yn-1-yl)oxy)hex-4-ynal (66)

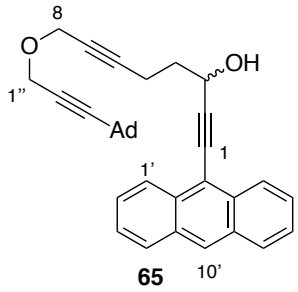


66

6-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)hex-4-yn-1-ol (**67**, 4.58 g, 16.0 mmol, 1.0 eq) in CH_2Cl_2 (200 mL) was cooled 0 °C and DMP (8.48 g, 20.0 mmol, 1.3 eq) was added in portions over 10 min. The resulting suspension was stirred at 0 °C for 4 h before warming to RT. The reaction mixture was washed with a mixture of aq. sat. $NaHCO_3$ (50 mL) and H_2O (200 mL). The

org. layer was separated and the aq. layer was extracted with CH_2Cl_2 (2x 100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column column chromatography (Et_2O/petrol ether, 1:1) to yield the title compound **66** as a slightly yellow oil (4.01 g, 88%): R_f 0.63 (Et_2O/*n*-pentane, 1:1); ν_{max} (neat): 2903s, 2851m, 2726w, 2362w, 2238w, 1728m, 1451m, 1347m, 1246w, 1184w, 1073s, 895w, 666w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.80 (1H, t, ^3J 1.1, C1*H*), 4.19 (2H, s, C1'*H*), 4.18 (2H, t, ^5J 2.1, C6*H*), 2.71–2.67 (2H, m, C2*H*), 2.58–2.53 (2H, m, C3*H*), 1.97–1.92 (3H, m, C3''*H*), 1.87–1.84 (6H, m, C2''*H*), 1.70–1.66 (6H, m, C4''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.4 (*C*1), 95.7 (*C*3'), 84.9 (*C*5), 76.6 (*C*4), 73.9 (*C*2'), 57.3 (*C*1'), 56.7 (*C*6), 42.8 (*C*2''), 42.5 (*C*2), 36.4 (*C*4''), 29.7 (*C*1''), 28.0 (*C*3''), 12.1 (*C*3); ESI-MS: m/z calc. for $C_{19}H_{24}O_2Na^+$ 307.1669 found 307.1665 [M+Na^+].

6.18.11. 8-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)-1-(anthracen-9-yl)octa-1,6-diyn-3-ol (65)

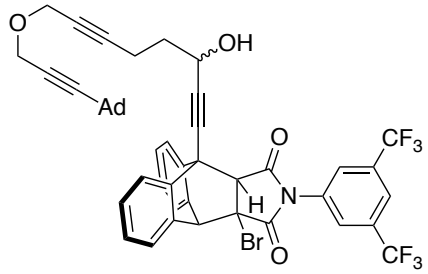


65

9-(2,2-Dibromovinyl)anthracene (**57**, 4.53 g, 12.5 mmol, 1.25 eq) in THF (150 mL) was cooled to –78 °C and *n*-BuLi (1.60 $molL^{-1}$ in hexanes, 15.6 mL, 25.0 mmol, 2.5 eq) was added dropwise. The mixture was stirred at –78 °C for 30 min before a solution of 6-((3-(adamantan-1-yl)prop-2-yn-1-yl)oxy)hex-4-ynal (**66**, 2.84 g, 10.0 mmol, 1.0 eq) in THF (50 mL) was added dropwise. After 1 h at –78 °C, the mixture was warmed to RT and stirred for 15 h. H_2O (200 mL), aq. sat. NH_4Cl (50 mL) and Et_2O (100 mL) were added. The org. layer was separated and the aq. layer was extracted with Et_2O (2x 100 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to yield the title compound **65** as a slightly yellow oil (3.19 g, 66%): R_f 0.23 (CH_2Cl_2); ν_{max} (neat): 3409w, 3053w, 2905s, 2851m, 2239w, 1444m, 1356m, 1071s, 910m, 846m, 735s, 617w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.49 (2H, dd, ^3J 8.7, ^4J 0.7, C1'*H*, C8'*H*), 8.42 (1H, s, C10'*H*), 7.99 (2H, d, ^3J 8.5, C4'*H*, C5'*H*), 7.60–7.54 (2H, m, C2'*H*, C7'*H*), 7.52–7.46 (2H, m, C3'*H*, C6'*H*), 5.09 (1H, dt, ^3J 6.2, 5.4, C3*H*), 4.25 (2H, s, C1''*H*), 4.24 (2H, t, ^5J 2.2, C8*H*), 2.72–2.57 (2H, m, C5*H*),

2.32 (1H, d, ^{3}J 5.4, O*H*), 2.23 (2H, dt, ^{3}J 7.0, 6.7, C4*H*), 1.96–1.90 (3H, m, C3'''*H*), 1.88–1.82 (6H, m, C2'''*H*), 1.68–1.63 (6H, m, C4'''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 132.8 (*C*8'a, *C*9'a), 131.2 (*C*4'a, *C*10'a), 128.8 (*C*4', *C*5'), 128.1 (*C*10'), 126.9 (*C*1', *C*8'), 126.6 (*C*2', *C*7'), 125.8 (*C*3', *C*6'), 116.4 (*C*9'), 100.7 (*C*2), 95.8 (*C*3''), 86.0 (*C*6), 82.2 (*C*1), 76.8 (*C*7), 74.0 (*C*2''), 62.5 (*C*3), 57.4 (*C*1''), 56.9 (*C*8), 42.9 (*C*2'''), 36.8 (*C*4), 36.4 (*C*4'''), 29.7 (*C*1'''), 28.1 (*C*3'''), 15.3 (*C*5); ESI-MS: m/z calc. for $C_{35}H_{34}O_2Na^+$ 509.2451 found 509.2452 [M+Na^+].

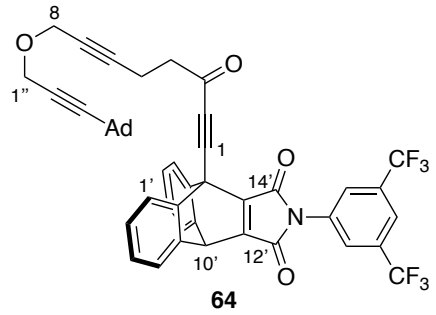
6.18.12. 9-(8-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)-3-hydroxyocta-1,6-diyn-1-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-11-bromo-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione (72)



72

8-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)-1-(anthracen-9-yl)octa-1,6-diyn-3-ol (**65**, 234 mg, 481 μmol, 1.0 eq) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-bromo-1*H*-pyrrole-2,5-dione (**54**, 280 mg, 721 μmol, 1.5 eq) were dissolved in *p*-xylene (5.0 mL) and the mixture was heated to 140 °C for 1.5 h. (caution: The reaction progress should be followed by NMR, because TLC is misleading). The reaction mixture was cooled to RT and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 1:2) to yield the title compound **72** as a yellow oil (348 mg, 83%): R_f 0.34 (Et_2O/*n*-pentane, 1:2); ν_{max} (neat): 2908m, 2240w, 1730s, 1468m, 1394m, 1280s, 1176s, 1141s, 1072m, 912w, 733m, 683w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91–7.86 (1H, m), 7.82 (1H, s), 7.79–7.75 (1H, m), 7.47 (1H, dd, *J* 7.1, 1.5), 7.42–7.28 (5H, m), 7.00 (2H, s), 4.98–4.91 (1H, m), 4.85 (1H, d, *J* 3.5), 4.25–4.19 (4H, m), 3.68 (2H, d, *J* 3.5), 2.73–2.60 (2H, m), 2.21 (2H, dt, *J* 6.9, 6.8), 1.96–1.90 (3H, m), 1.88–1.83 (6H, m), 1.69–1.63 (6H, m); Purification of the product turned out to be crucial due to side reactions with remaining dienophile in the subsequent reaction.

6.18.13. 9-(8-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)-3-oxoocta-1,6-diyn-1-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-9,10-dihydro-9,10-[3,4]epipyrrolo-anthracene-12,14-dione (64)

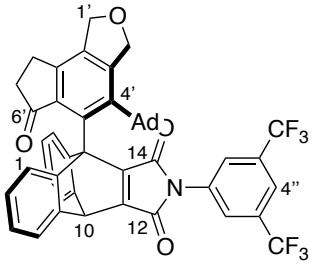


64

9-(8-((3-(Adamantan-1-yl)prop-2-yn-1-yl)oxy)-3-hydroxyocta-1,6-diyn-1-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-11-bromo-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione (**72**, 350 mg, 400 µmol, 1.0 eq) was dissolved in $CDCl_3$ (12 mL). Et_3N (562 µL, 4.00 mmol, 10 eq) was added and the mixture was stirred at RT for 6 h. The reaction mixture was washed with aq. HCl (1.00 $molL^{-1}$, 30 mL) and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2x 20 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. DMP (212 mg, 500 µmol, 1.3 eq) was added and the suspension was warmed to RT and stirred for 2 h. The reaction mixture was washed with aq. sat. $NaHCO_3$ (50 mL). The org. layer was separated and the aq. layer was extracted with CH_2Cl_2 (2x 30 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to yield the title compound **64** as a slightly yellow oil (205 mg, 65%): R_f 0.69 (CH_2Cl_2); ν_{max} (neat): 2908w, 2234w, 1730s, 1686m, 1470m, 1392s, 1279s, 1182m, 1138s, 1074m, 910w, 730m, 638w; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (3H, s, Ar*H*), 7.75 (2H, dd, ^3J 7.3, ^4J 1.4, C4'*H*, C5'*H*), 7.49 (2H, dd, ^3J 7.1, ^4J 1.3, C1'*H*, C8'*H*), 7.22–7.13 (4H, m, C2'*H*, C3'*H*, C6'*H*, C7'*H*), 5.62 (1H, s, C10'*H*), 4.21 (2H, s, C1''*H*), 4.20 (2H, t, ^5J 2.2, C8*H*), 3.16 (2H, t, ^3J 7.0, C4*H*), 2.79 (2H, tt, ^3J 7.1, ^5J 2.1, C5*H*), 1.95–1.90 (3H, m, C3'''*H*), 1.87–1.81 (6H, m, C2'''*H*), 1.70–1.62 (6H, m, C4'''*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 185.0 (*C*3), 163.4 (*C*14'), 162.7 (*C*12'), 156.7 (*C*15'), 152.7 (*C*11'), 142.3 (*C*8'a, *C*9'a), 142.1 (*C*4'a, *C*5'a), 133.3, 132.6 (q, $^2J_{C–F}$ 34.0), 126.9 (C3', C6'), 126.4 (*C*2', *C*7'), 126.2, 125.0 (*C*4', *C*5'), 123.5 (*C*1', *C*8'), 122.9 (q, $^1J_{C–F}$ 273, *C*F_3), 121.4 (m), 95.8 (*C*3''), 89.5 (*C*2), 84.7 (*C*6), 82.7 (*C*1), 77.0 (*C*7), 74.0 (*C*2''), 57.4 (*C*1''), 56.8 (*C*8),

49.4 (*C*9'), 46.6 (*C*10'), 44.7 (*C*4), 42.9 (*C*2'''), 36.4 (*C*4'''), 29.7 (*C*1'''), 28.1 (*C*3'''), 13.8 (*C*5); ESI-MS: m/z calc. for $C_{48}H_{40}F_6NO_5^+$ 824.2805 found 824.2790 [M+H$^+$].

6.18.14. 9-(4-(Adamantan-1-yl)-6-oxo-3,6,7,8-tetrahydro-1*H*-indeno[4,5-c]-furan-5-yl)-13-(3,5-bis(trifluoromethyl)phenyl)-9,10-dihydro-9,10-[3,4]epi-pyrroloanthracene-12,14-dione (73)



(*ap*)-**73**

Representative procedure for Rh-catalyzed enantioselective [2 + 2 + 2] cycloaddition: $[Rh(cod)_2]BF_4$ (4.06 mg, 10.0 µmol, 20 mol%) and (*S*)-xyl-SDP (**lig10**, 7.01 mg, 10.0 µmol, 20 mol%) were dissolved in CH_2Cl_2 (5.0 mL) and the mixture was stirred at room temperature for 30 min. H_2 was introduced to the resulting solution and after stirring for 1 h at RT, the resulting solution was concentrated *in vacuo*. The residue was dissolved in toluene (16.5 mL) and heated to 60 °C. The triyne (**46**, 39.6 mg, 50.0 µmol, 1.0 eq) was added in three portions over 1 h and the resulting mixture was stirred for 6 h at 60 °C. The mixture was cooled to RT and concentrated *in vacuo*. The crude product was purified by column chromatography (Et_2O/*n*-pentane, 1:1) to yield the title compund (*ap*)-**73** as a colourless oil (29.8 mg, 75% yield, e.r. = 93:7): R_f 0.26 (Et_2O/*n*-pentane, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (2H, s, C2''*H*, C6''*H*), 7.78 (1H, s, C4''*H*), 7.58–7.55 (1H, m, C4*H*), 7.35 (1H, dd, ^3J 7.3, ^4J 1.2, C5*H*), 7.32–7.27 (2H, m, C1*H*, C3*H*), 7.13 (1H, ddd, ^3J 7.6, 7.5, ^4J 1.2, C2*H*), 6.92 (1H, d, ^3J 7.8, C8*H*), 6.84 (1H, ddd, ^3J 7.4, 7.3, ^4J 1.2, C6*H*), 6.71 (1H, ddd, ^3J 7.7, 7.6, ^4J 1.3, C7*H*), 5.83 (1H, d, *J* 12.7), 5.65 (1H, d, *J* 12.8), 5.48 (1H, s, C10*H*), 5.27–5.19 (2H, m), 3.08–2.93 (2H, m, C8'*H*), 2.57–2.38 (2H, m, C7'*H*), 2.06–1.97 (3H, C3'''*H*), 1.87–1.79 (6H, m, C2'''*H*), 1.62–1.44 (6H, m, C4'''*H*); ^{13}C NMR (126 MHz, $CDCl_3$, extracted from HMBC) δ = 202.2 (*C*6), 175.2 (*C*14), 150.7 (*C*8a), 146.2 (*C*10a), 145.3 (*C*3'a), 144.9 (*C*9a), 135.7 (*C*4a), 133.5 (*C*1''), 128.0 (*C*1), 127.0 (*C*3), 125.8 (*C*2''), 125.1 (*C*5), 124.7 (*C*2), 124.6 (*C*6), 124.1 (*C*4), 124.0 (*C*7), 123.8 (*C*8), 121.1 (*C*4''), 62.1 (*C*9), 47.7 (*C*10), 37.0 (*C*7'), 23.1 (*C*7'); ^{1}H ^{1}H NOESY (500 MHz, $CDCl_3$): C6'*H*–C8*H*, C1*H*–C2'''*H*, C1*H*–C3'''*H*,

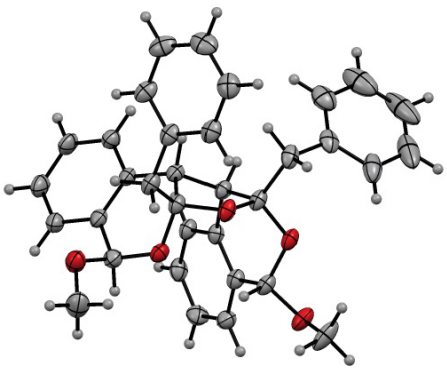
C2'''*H*–C2''*H*, C4'''*H*C2''*H*; ESI-MS: m/z calc. for $C_{47}H_{35}F_6NO_4Na^+$ 814.2362 found 814.2354 [M+Na^+]; The e.r of 93:7 of (*ap*)-**73** was determined by HPLC using a *Chiralcel IC-B* analytical column (1.0 $mLmin^{-1}$, *i*-PrOH/*n*-heptane, 5:95): major t_R = 15.4 min and minor t_R = 23.4 min; racemic reference material was obtained with *rac*-BINAP as ligand.

6.19. X-ray Crystallographic Analysis (by Dr. Markus Neuburger and Dr. Alessandro Prescimone)

6.19.1. X-ray of (*meso*)-5

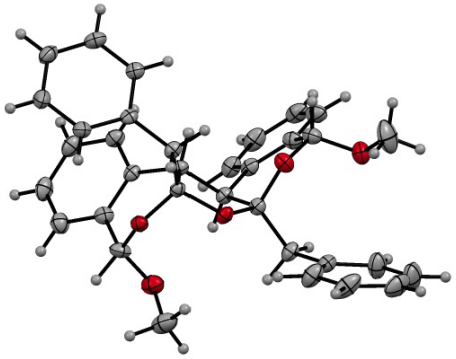
The crystal was measured on a Stoe StadiVari diffractometer at 123K using Graded multilayer mirror-monochromated Ga K_α-radiation with λ = 1.34143 Å, Θ_{max} = 55.969°. Minimal/maximal transmission 0.98/0.99, μ = 0.422 mm^{-1}. The STOE X-AREA suite has been used for datacollection and integration. From a total of 56746 reflections, 10475 were independent (merging r = 0.065). From these, 7186 were considered as observed (I>2.0σ(I)) and were used to refine 703 parameters. The structure was solved by Other methods using the program Superflip. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0495 (observed data), wR = 0.1121 (all data), GOF = 0.8759. Minimal/maximal residual electron density = -0.24/0.32 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.

Chemical formula	$C_{34}H_{32}O_5$
Formula weight	520.62
Z	4
$D_{calc.}$	1.246 Mg · m^{-3}
F(000)	1104
Crystal description	colourless block
Crystal size	0.030 · 0.090 · 0.110 mm^3
Absorption coefficient	0.422 mm^1
min/max transmission	0.98 / 0.99
Temperature	123K
Radiation (wavelength)	Ga K_α (λ = 1.34143 Å)
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	a = 12.1680(4) Å b = 13.4704(4) Å c = 18.3808(5) Å α = 72° β = 81° γ =77°
Volume	2774.84(15) $Å^3$
min/max Θ	3.228° / 55.969°
Number of collected reflections	56746
Number of independent refections	10475 (merging r = 0.065)
Number of observed reflections	7186 (I>2.0σ(I))
Number of refined parameters	703
R	0.0495
wR	0.1121
Goodness of fit	0.8759



6.19.2. X-ray of (*rac*)-5

The crystal was measured on a Stoe StadiVari diffractometer at 123K using Graded multilayer mirror-monochromated GaK_α-radiation with λ = 1.34143 Å, Θ_{max}= 55.941°. Minimal/maximal transmission 0.98/0.99, μ = 0.436 mm^{-1}. The STOE X-AREA suite has been used for datacollection and integration. From a total of 62038 reflections, 5177 were independent (merging r = 0.031). From these, 3896 were considered as observed (I>2.0σ(I)) and were used to refine 371 parameters. The structure was solved by Other methods using the program Superflip. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0478 (observed data), wR = 0.0705 (all data), GOF = 0.8530. Minimal/maximal residual electron density = -0.51/0.86 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.

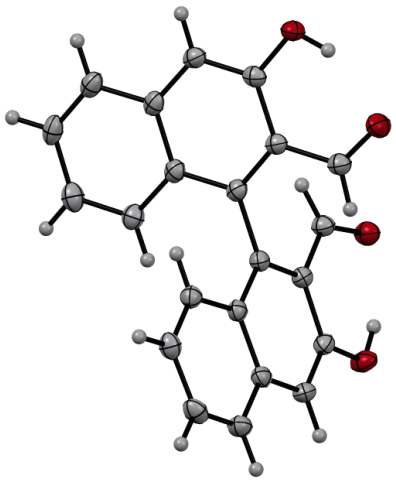


Chemical formula	$C_{34}H_{32}O_5$
Formula weight	520.62
Z	4
$D_{calc.}$	1.287 Mg · m^{-3}
F(000)	1104
Crystal description	colourless block
Crystal size	0.020 · 0.110 · 0.130 mm^3
Absorption coefficient	0.436 mm^1
min/max transmission	0.98 / 0.99
Temperature	123K
Radiation (wavelength)	Ga K_α (λ = 1.34143 Å)
Crystal system	monoclinic
Space group	P 2_1
Unit cell dimensions	a = 9.9868(3) Å b = 22.1830(7) Å c = 13.0926(3) Å α = 90° β = 112° γ = 90°
Volume	2686.80(14) $Å^3$
min/max Θ	3.614° / 55.941°
Number of collected reflections	62038
Number of independent refections	5177 (merging r = 0.031)
Number of observed reflections	3896 (I>2.0σ(I))
Number of refined parameters	371
R	0.0478
wR	0.0705
Goodness of fit	0.8530

6.19.3. X-ray of (R_a)-14a (CCDC1856452)

The crystal was measured on a Bruker Kappa Apex2 diffractometer at 123K using graphite-monochromated Cu Kα -radiation with λ = 1.54178 Å, Θ_{max} = 69.037°. Minimal/maximal transmission 0.88/0.92, μ = 0.802 mm^1. The Apex2 suite has been used for datacollection and integration. From a total of 17422 reflections, 1479 were independent (merging r = 0.026). From these, 1479 were considered as observed (I>2.0σ (I)) and were used to refine 123 parameters. The structure was solved by Other methods using the program Superflip. Least-squares refinement against F was carried out on all nonhydrogen atoms using the program CRYSTALS. R = 0.0246 (observed data), wR = 0.0229 (all data), GOF = 0.9973. Minimal/maximal residual electron density = -0.17/0.14 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.

Chemical formula	$C_{22}H_{14}O_4$
Formula weight	342.35
Z	4
$D_{calc.}$	1.424 Mg · m^{-3}
F(000)	712
Crystal description	colourless block
Crystal size	0.100 · 0.160 · 0.220 mm^3
Absorption coefficient	0.802 mm^1
min/max transmission	0.88 / 0.92
Temperature	123K
Radiation (wavelength)	Ga $K_α$ (λ = 1.54178 Å)
Crystal system	orthorombic
Space group	P 2 2 2_1
Unit cell dimensions	a = 10.4697(3) Å b = 14.4748(17) Å c = 10.5350(12) Å α = 90° β = 90° γ = 90°
Volume	1596.5(3) $Å^3$
min/max Θ	5.214° / 69.037°
Number of collected reflections	17422
Number of independent refections	1479 (merging r = 0.026)
Number of observed reflections	1479 (I>2.0σ(I))
Number of refined parameters	123
R	0.0246
wR	0.0229
Goodness of fit	0.9973
Flack	0.08(7)

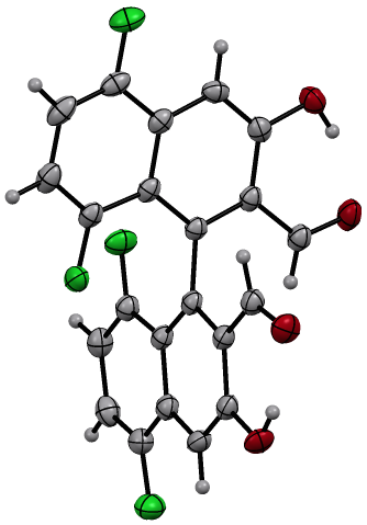


Reflection of (R_a)-**14a**

6.19.4. X-ray of (S_a)-14c (CCDC1856453)

The crystal was measured on a Stoe StadiVari diffractometer at 123K using Graded multilayer mirror-monochromated Ga K_α -radiation with $\lambda = 1.34143$ Å, $\Theta_{max} = 59.261°$. Minimal/maximal transmission 0.95/0.96, $\mu = 0.789$ mm^{-1}. The STOE X-AREA suite has been used for datacollection and integration. From a total of 24644 reflections, 5661 were independent (merging r = 0.018). From these, 5599 were considered as observed (I>2.0σ (I)) and were used to refine 558 parameters. The structure was solved by Other methods using the program Superflip. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0382 (observed data), wR = 0.0447 (all data), GOF = 0.9920. Minimal/maximal residual electron density = -0.23/0.23 e Å^{-3}. Chebychev polynomial weights were used to complete the refinement.

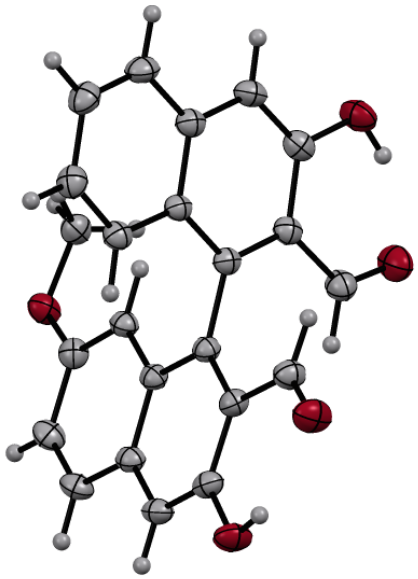
Chemical formula	$C_{22}H_{10}F_4O_4$
Formula weight	414.31
Z	2
$D_{calc.}$	1.641 Mg · m^{-3}
F(000)	420
Crystal description	colourless needle
Crystal size	0.050 · 0.070 · 0.170 mm^3
Absorption coefficient	0.789 mm^1
min/max transmission	0.95 / 0.96
Temperature	123K
Radiation (wavelength)	Ga K_α ($\lambda = 1.34143$ Å)
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	a = 7.1581(2) Å b = 9.9418(3) Å c = 12.4859(3) Å α = 93° β = 98° γ = 107°
Volume	838.64(4) Å^3
min/max Θ	3.126° / 59.261°
Number of collected reflections	24644
Number of independent refections	5661 (merging r = 0.018)
Number of observed reflections	5599 (I>2.0σ(I))
Number of refined parameters	558
R	0.0382
wR	0.0447
Goodness of fit	0.992
Flack	–0.02(10)



6.19.5. X-ray of (S_a)-14g (CCDC185645)

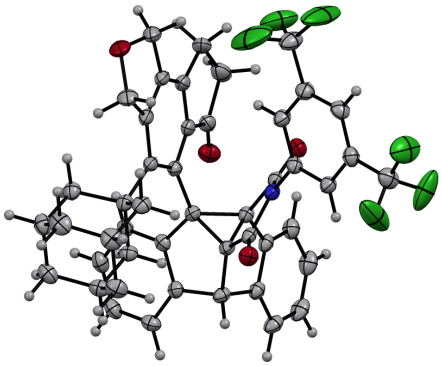
The crystal was measured on a Stoe StadiVari diffractometer at 123K using Graded multilayer mirror-monochromated Ga K_α -radiation with λ = 1.34143 Å, Θ_{max} = 59.456°. Minimal/maximal transmission 0.95/0.97, μ = 0.529 mm^{-1}. The STOE X-AREA suite has been used for datacollection and integration. From a total of 24887 reflections, 3792 were independent (merging r = 0.029). From these, 3767 were considered as observed (I>2.0σ (I)) and were used to refine 262 parameters. The structure was solved by Other methods using the program Superflip. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0354 (observed data), wR = 0.0389 (all data), GOF = 1.0901. Minimal/maximal residual electron density = -0.18/0.17 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.

Chemical formula	$C_{22}H_{16}O_5$
Formula weight	372.38
Z	4
$D_{calc.}$	1.429 Mg · m^{-3}
F(000)	776
Crystal description	yellow block
Crystal size	0.060 · 0.090 · 0.190 mm^3
Absorption coefficient	0.529 mm^1
min/max transmission	0.95 / 0.97
Temperature	123K
Radiation (wavelength)	Ga K_α (λ = 1.34143 Å)
Crystal system	orthorombic
Space group	P 2_1 2_1 2_1
Unit cell dimensions	a = 9.7359(2) Å b = 10.6100(2) Å c = 16.7543(3) Å α = 90° β = 90° γ = 90°
Volume	1730.68(6) $Å^3$
min/max Θ	4.291° / 59.456°
Number of collected reflections	24887
Number of independent refections	3792 (merging r = 0.029)
Number of observed reflections	3767 (I>2.0σ(I))
Number of refined parameters	262
R	0.0354
wR	0.0389
Goodness of fit	1.0901
Flack	0.0(2)



6.19.6. X-ray of 74

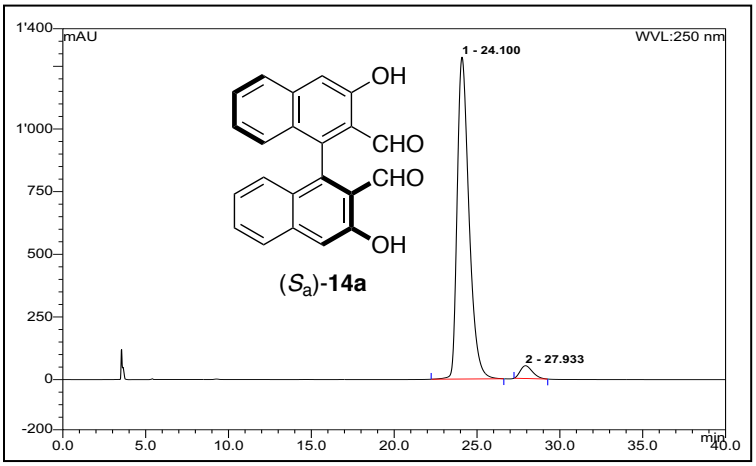
The crystal was measured on a Bruker APEX-II CCD diffractometer at 130K using graphite-monochromated CuK_α-radiation with λ = 1.54178 Å, Θ_{max}= 70.326°. Minimal/maximal transmission 0.6973/0.7533, μ = 0.922 mm^{-1}. The Apex2 suite has been used for datacollection and integration. From a total of 50074 reflections, 7461 were independent (merging r = 0.0402). From these, 7461 were considered as observed ($I > 2\sigma(I)$) and were used to refine 562 parameters. The structure was solved by dual methods using the program SHELXT 2014/5. Least-squares refinement against Fsqd was carried out on all non-hydrogen atoms using the program ShelXL. R = 0.0748 (observed data), wR = 0.1943 (all data), GOF = 1.073. Minimal/maximal residual electron density = -0.582/0.878 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.



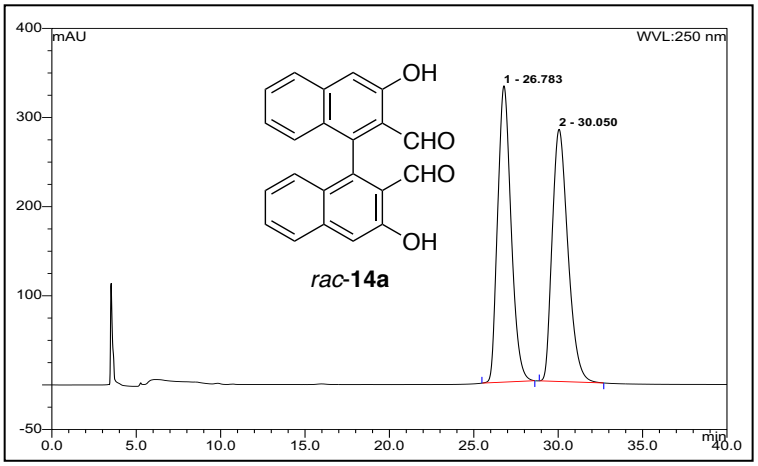
Chemical formula	$C_{50}H_{43}F_6NO_5$
Formula weight	851.85
Z	4
$D_{calc.}$	1.417 Mg · m^{-3}
F(000)	1776
Crystal description	clear light colourless block
Crystal size	0.110 · 0.160 · 0.190 mm^3
Absorption coefficient	0.922 mm^1
min/max transmission	0.70 / 0.75
Temperature	123K
Radiation (wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system	monoclinic
Space group	P 2
Unit cell dimensions	a = 9.2157(7) Å b = 16.6797(12) Å c = 26.1243(18) Å α = 90° β = 97° γ = 90°
Volume	3992.3(5) $Å^3$
min/max Θ	3.149° / 70.046°
Number of collected reflections	50074
Number of independent refections	7461 (merging r = 0.0402)
Number of observed reflections	7461 ($I>2.0\sigma(I)$)
Number of refined parameters	562
R	0.0748
wR	0.1943
Goodness of fit	1.073

6.20. HPLC-Data

6.20.1. (S_a)- 14a

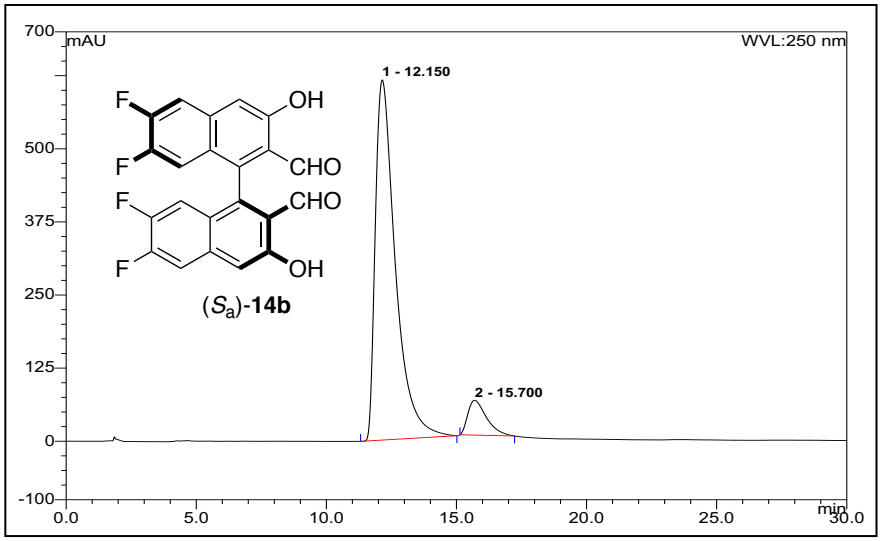


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	24.10	n.a.	1284.089	1060.810	96.05
2	27.93	n.a.	51.014	43.672	3.95
Total:			1335.104	1104.482	100.00

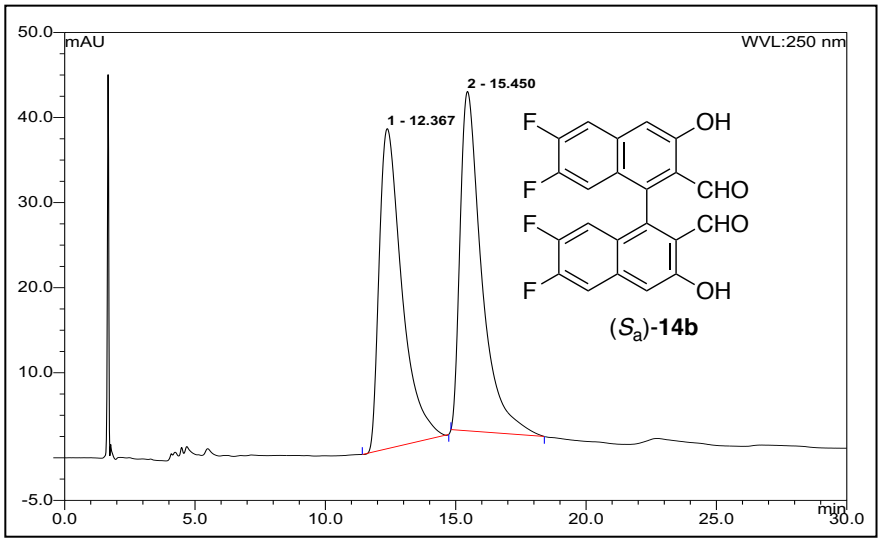


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	26.78	n.a.	332.466	306.265	50.04
2	30.05	n.a.	282.999	305.716	49.96
Total:			615.464	611.981	100.00

6.20.2. (S_a)-14b

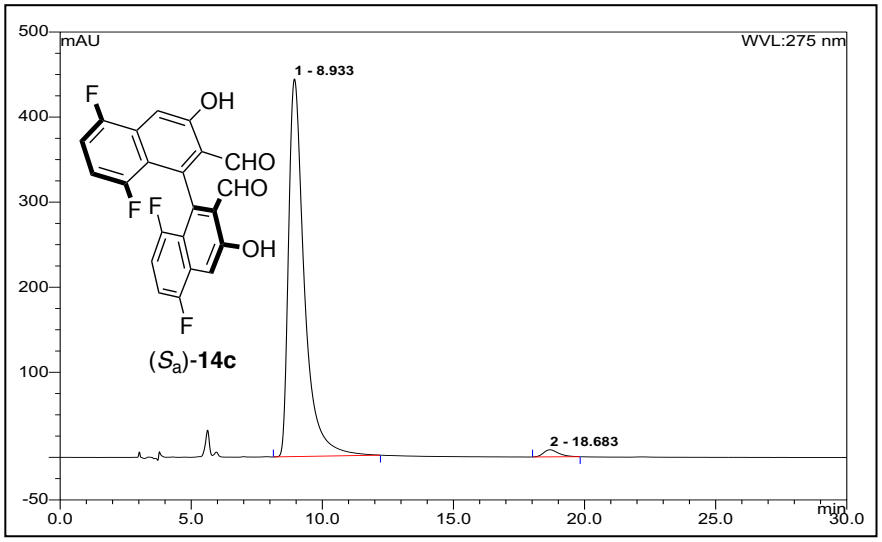


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	12.15	n.a.	615.757	550.918	91.77
2	15.70	n.a.	59.414	49.410	8.23
Total:			675.171	600.328	100.00

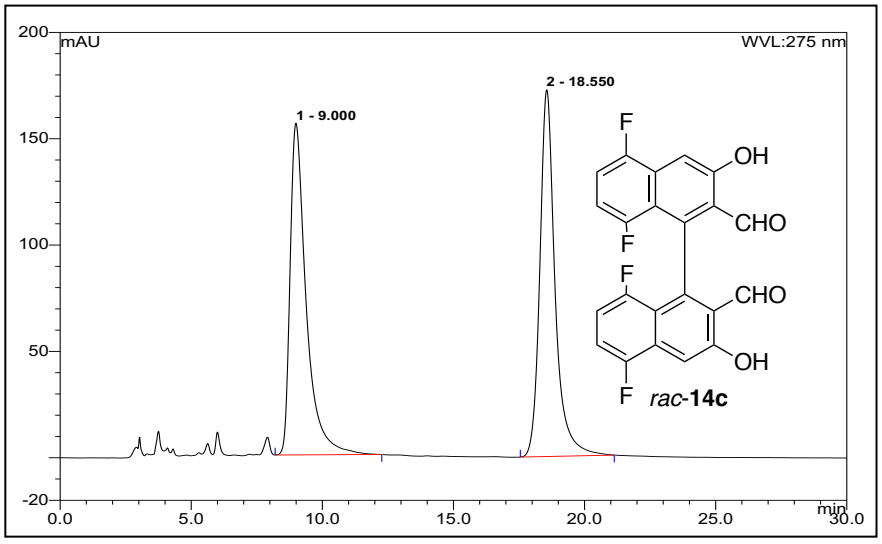


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	12.37	n.a.	37.622	38.041	49.85
2	15.45	n.a.	39.893	38.274	50.15
Total:			77.514	76.315	100.00

6.21. (S_a)-14c

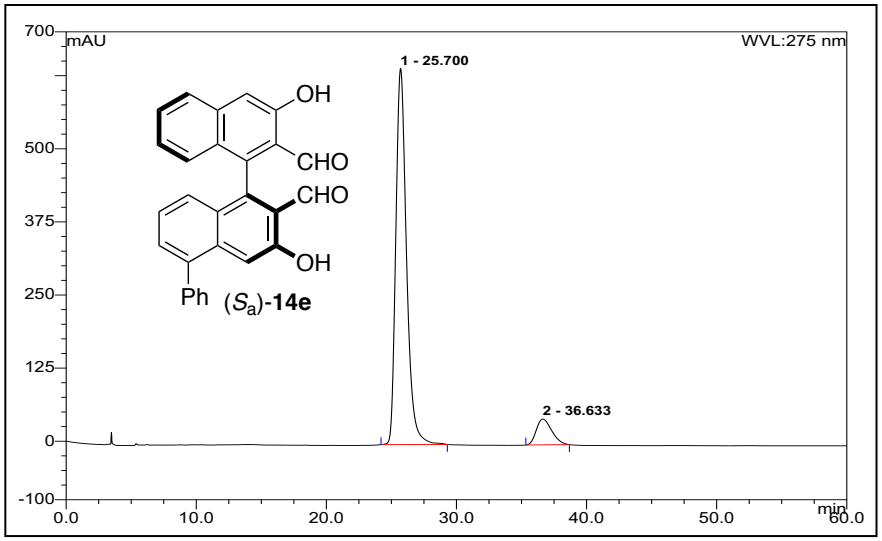


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	8.93	n.a.	443.911	309.298	98.23
2	18.68	n.a.	8.321	5.563	1.77
Total:			452.232	314.861	100.00

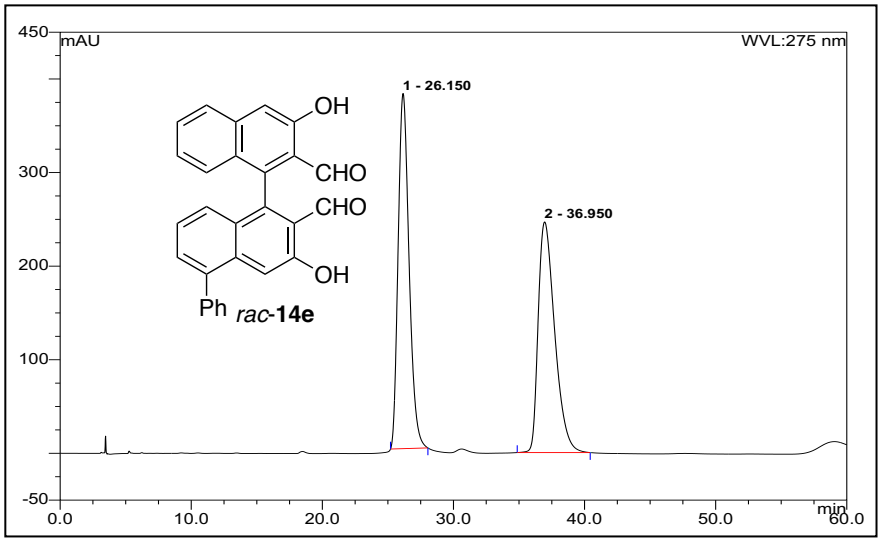


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	9.00	n.a.	155.949	111.138	48.91
2	18.55	n.a.	172.418	116.070	51.09
Total:			328.367	227.208	100.00

6.21.1. (S_a)-14e

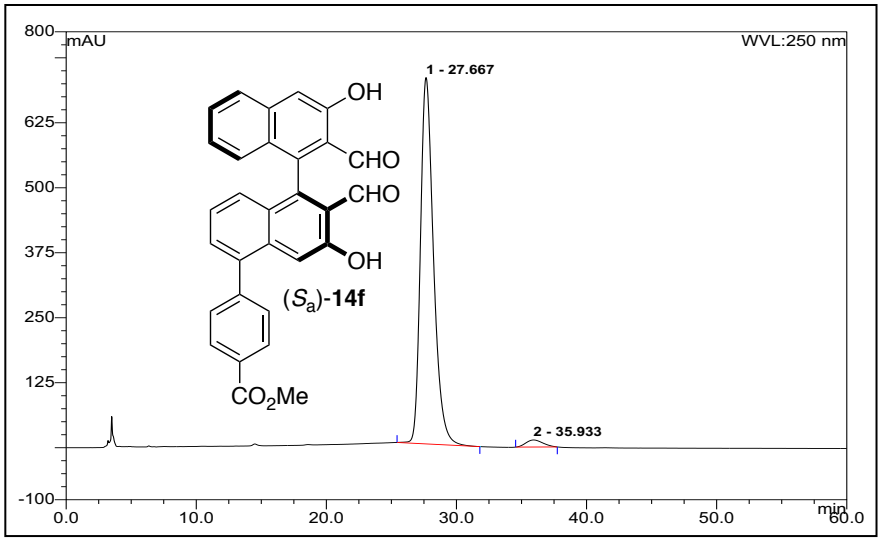


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	25.70	n.a.	643.104	612.697	91.00
2	36.63	n.a.	44.079	60.607	9.00
Total:			687.183	673.304	100.00

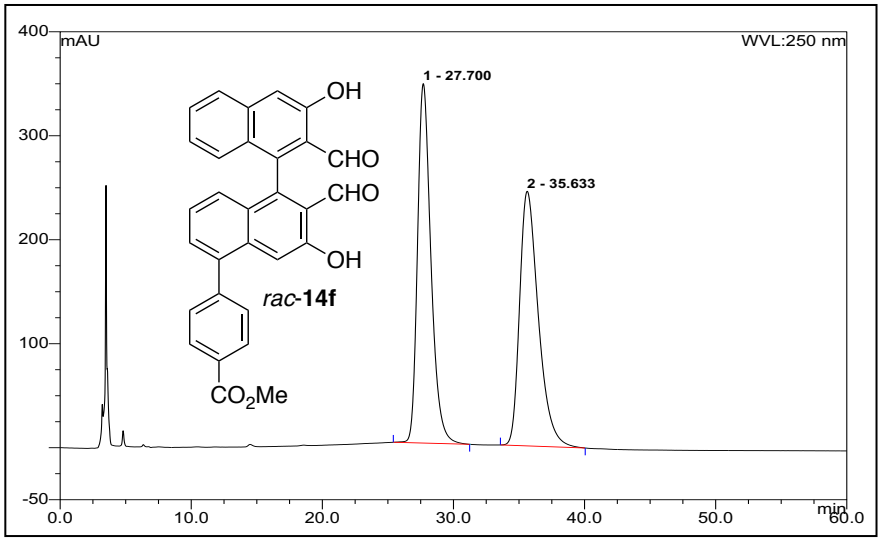


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	26.15	n.a.	379.562	366.602	50.51
2	36.95	n.a.	246.446	359.158	49.49
Total:			626.008	725.760	100.00

6.21.2. (S_a)-14f

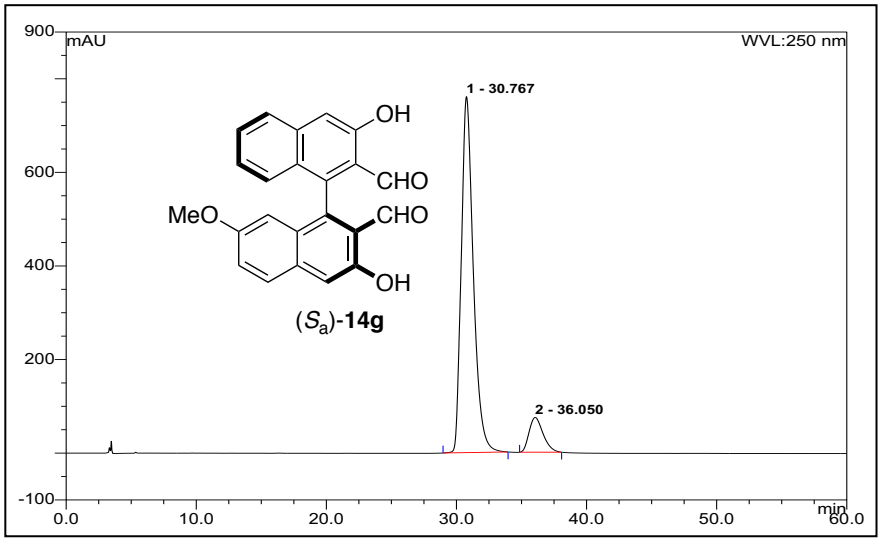


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	27.67	n.a.	704.670	820.024	97.55
2	35.93	n.a.	13.543	20.576	2.45
Total:			718.213	840.599	100.00

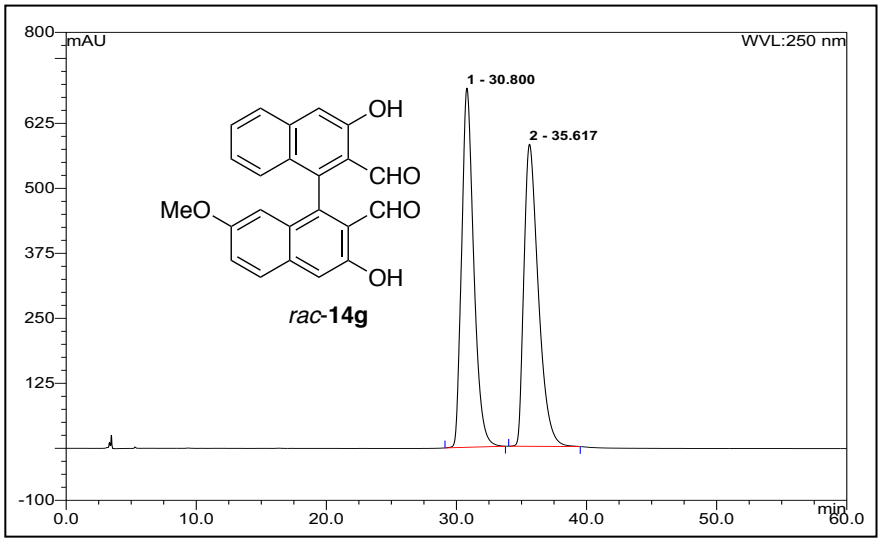


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	27.70	n.a.	345.669	410.283	50.30
2	35.63	n.a.	244.878	405.422	49.70
Total:			590.548	815.705	100.00

6.22. (S_a)- 14g

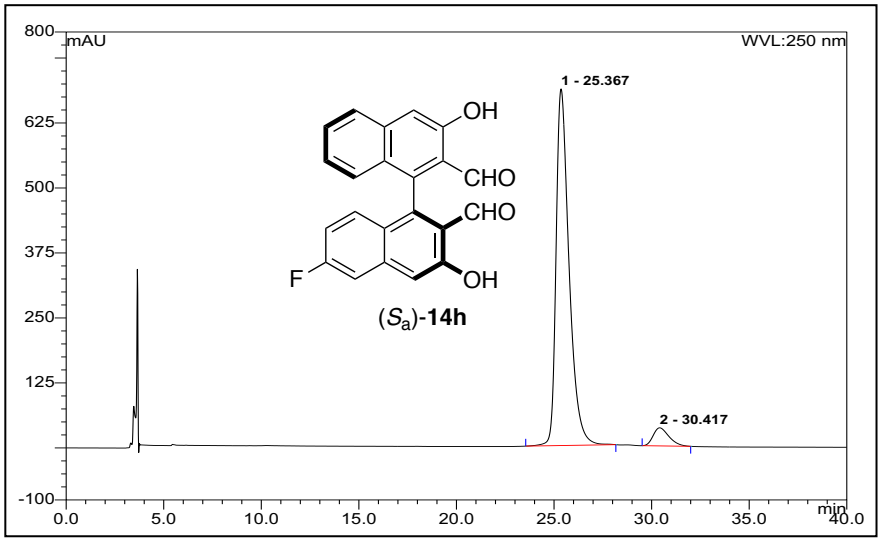


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	30.77	n.a.	760.778	816.224	89.80
2	36.05	n.a.	74.230	92.727	10.20
Total:			835.008	908.951	100.00

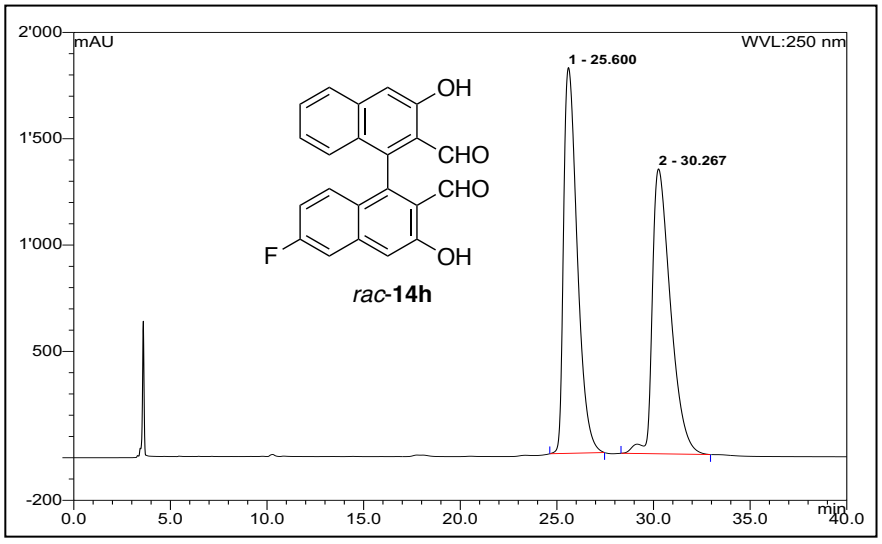


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	30.80	n.a.	690.978	746.509	50.04
2	35.62	n.a.	581.071	745.265	49.96
Total:			1272.049	1491.774	100.00

6.23. (S_a)-14h

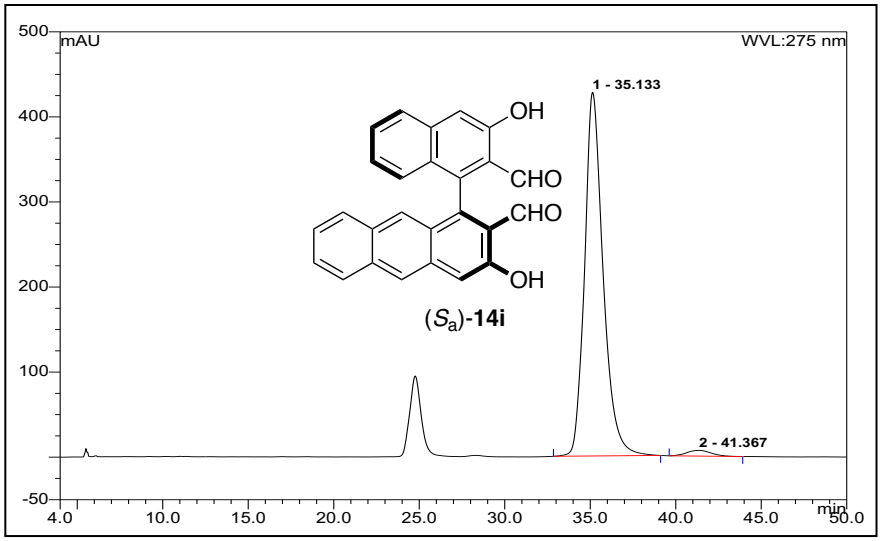


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	25.37	n.a.	685.893	529.146	94.20
2	30.42	n.a.	34.791	32.554	5.80
Total:			720.684	561.700	100.00

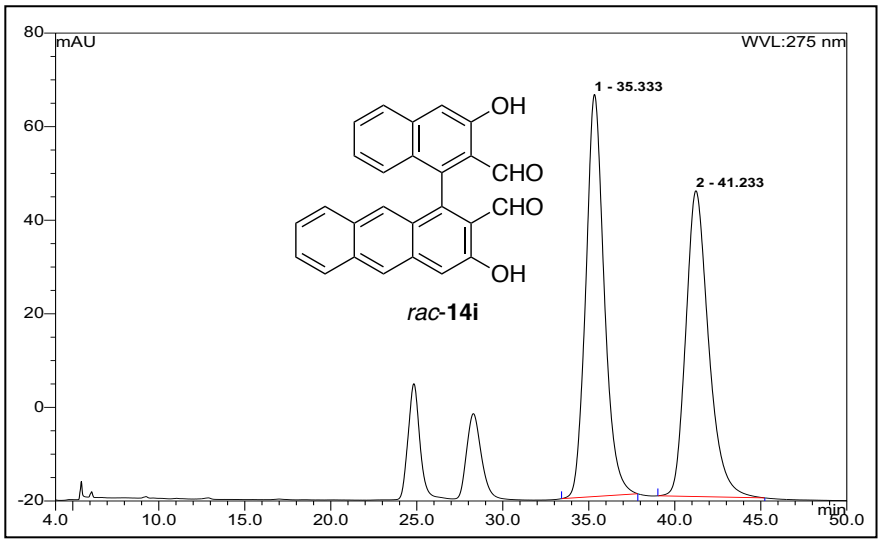


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	25.60	n.a.	1813.588	1488.494	50.35
2	30.27	n.a.	1339.684	1467.792	49.65
Total:			3153.272	2956.286	100.00

6.23.1. (S_a)-14i

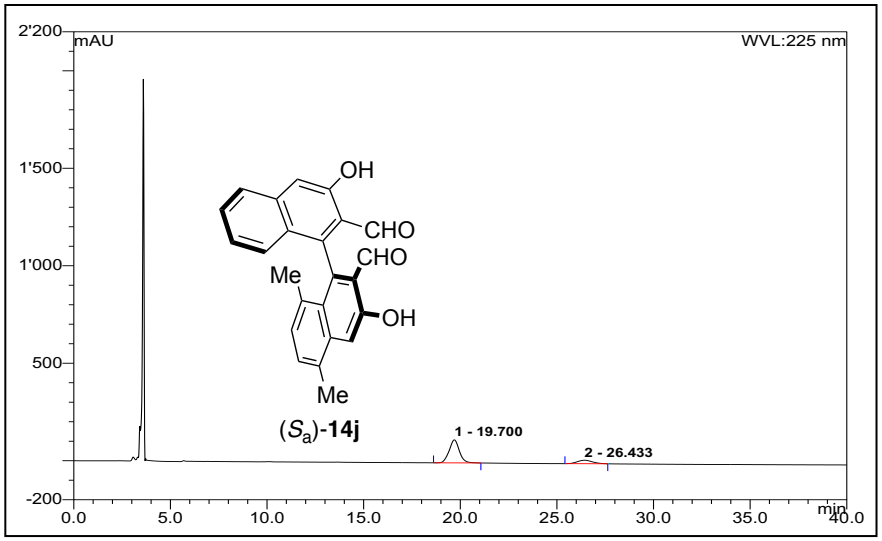


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	35.13	n.a.	427.412	537.828	97.98
2	41.37	n.a.	6.735	11.090	2.02
Total:			434.147	548.918	100.00

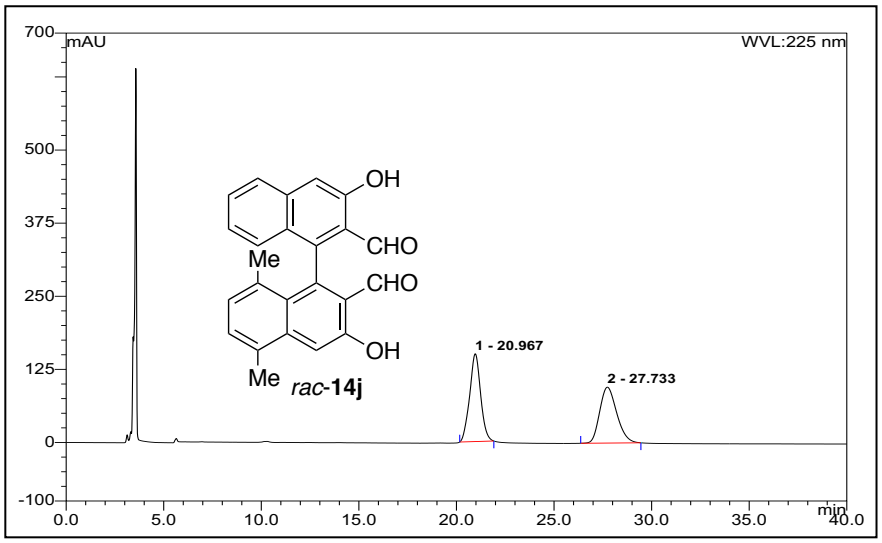


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	35.33	n.a.	85.933	106.499	51.51
2	41.23	n.a.	65.345	100.256	48.49
Total:			151.278	206.756	100.00

6.23.2. (S_a)-14j

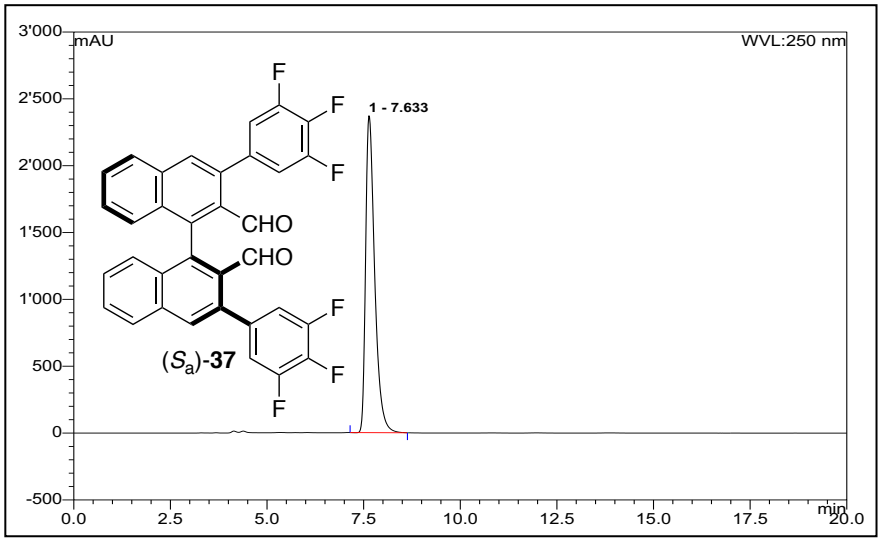


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	19.70	n.a.	117.972	72.163	81.79
2	26.43	n.a.	17.882	16.063	18.21
Total:			135.854	88.227	100.00

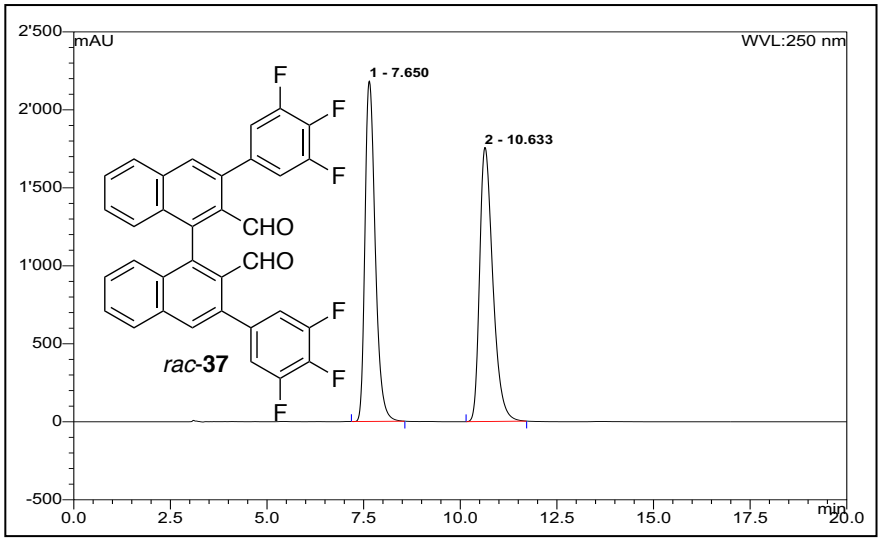


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	20.97	n.a.	150.112	97.859	50.37
2	27.73	n.a.	95.587	96.441	49.63
Total:			245.699	194.300	100.00

6.24. (S_a)-37

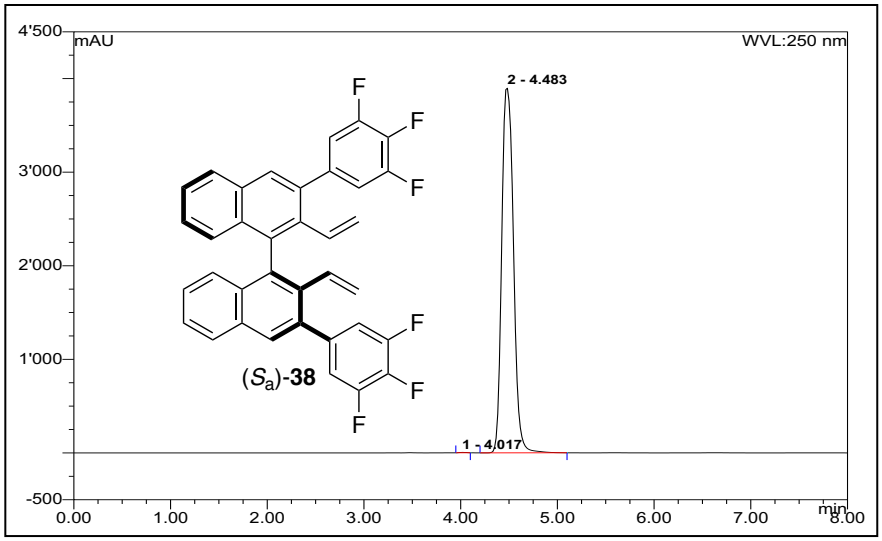


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	7.63	n.a.	2369.886	645.013	100.00
Total:			2369.886	645.013	100.00

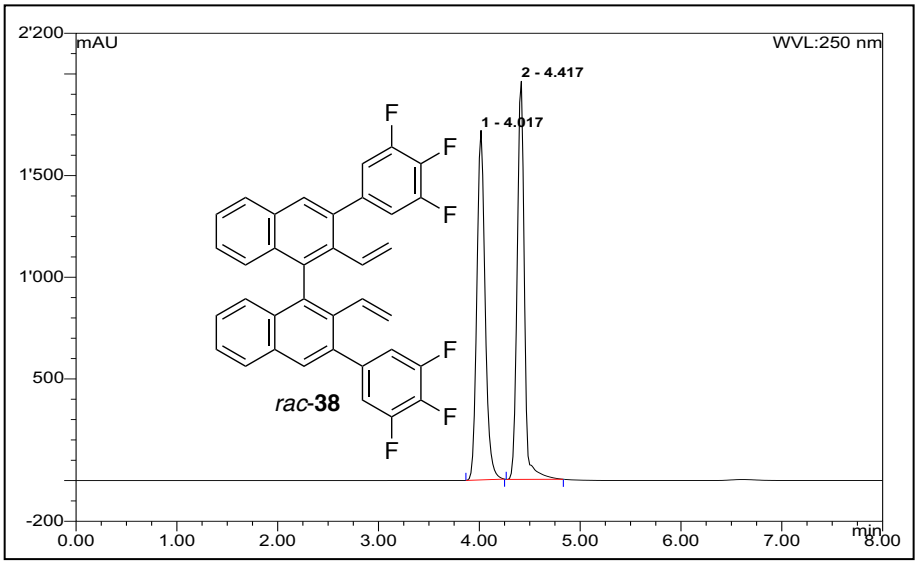


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	7.65	n.a.	2183.478	672.333	49.11
2	10.63	n.a.	1757.010	696.765	50.89
Total:			3940.488	1369.098	100.00

6.24.1. (S_a)-38

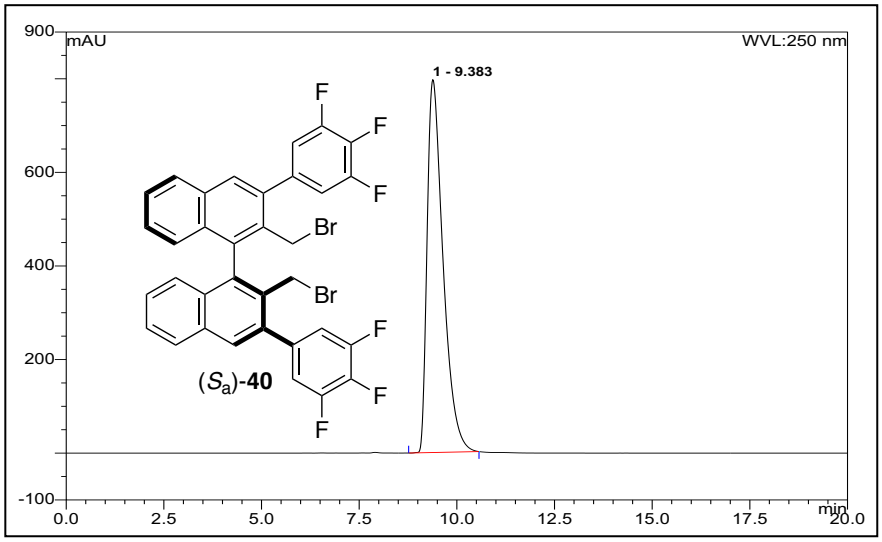


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	4.02	n.a.	3.897	0.320	0.06
2	4.48	n.a.	3897.190	550.495	99.94
Total:			3901.087	550.815	100.00

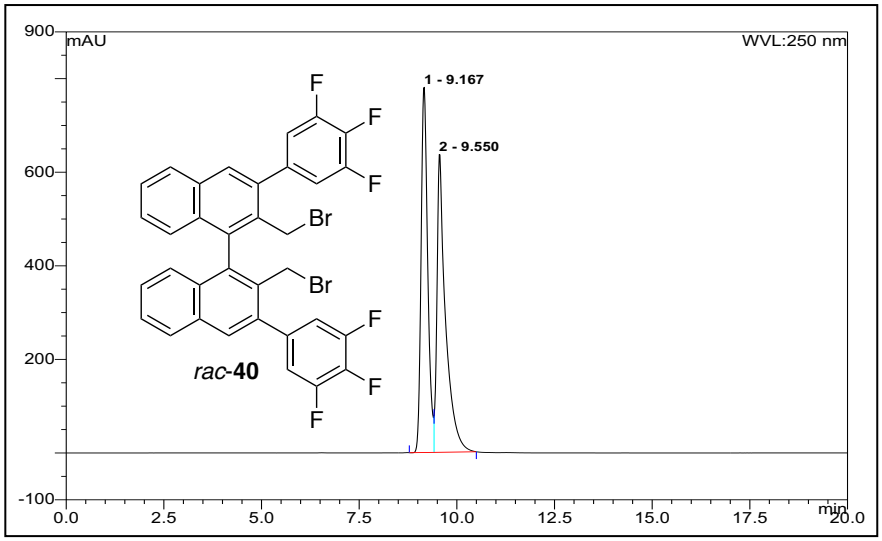


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	4.02	n.a.	1718.879	162.854	50.19
2	4.42	n.a.	1957.919	161.630	49.81
Total:			3676.798	324.484	100.0

6.25. (S_a)-40

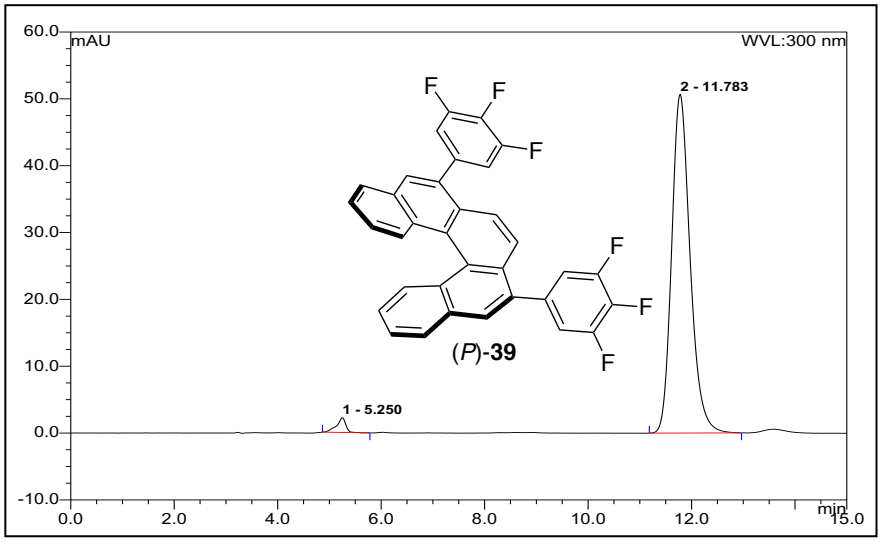


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	9.38	n.a.	796.999	377.023	100.00
Total:			796.999	377.023	100.00

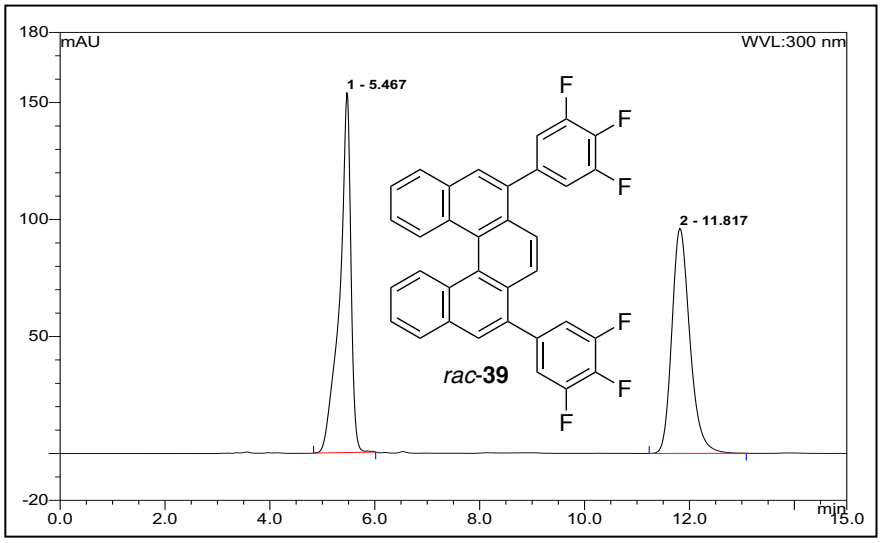


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	9.17	n.a.	780.591	154.705	48.79
2	9.55	n.a.	636.594	162.371	51.21
Total:			1417.184	317.076	100.00

6.26. (*P*)-39

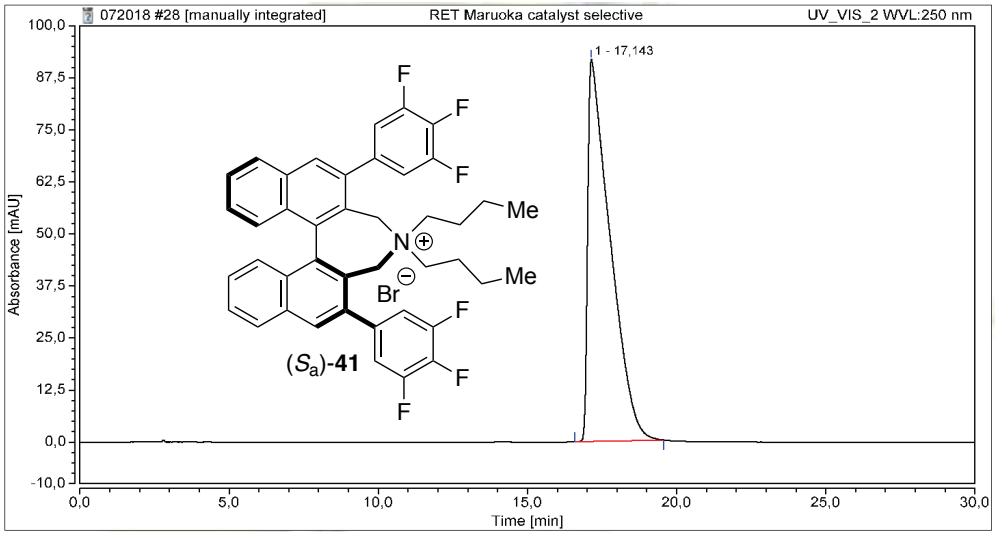


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	5.25	n.a.	2.208	0.455	2.12
2	11.78	n.a.	50.666	20.963	97.88
Total:			52.874	21.418	100.00

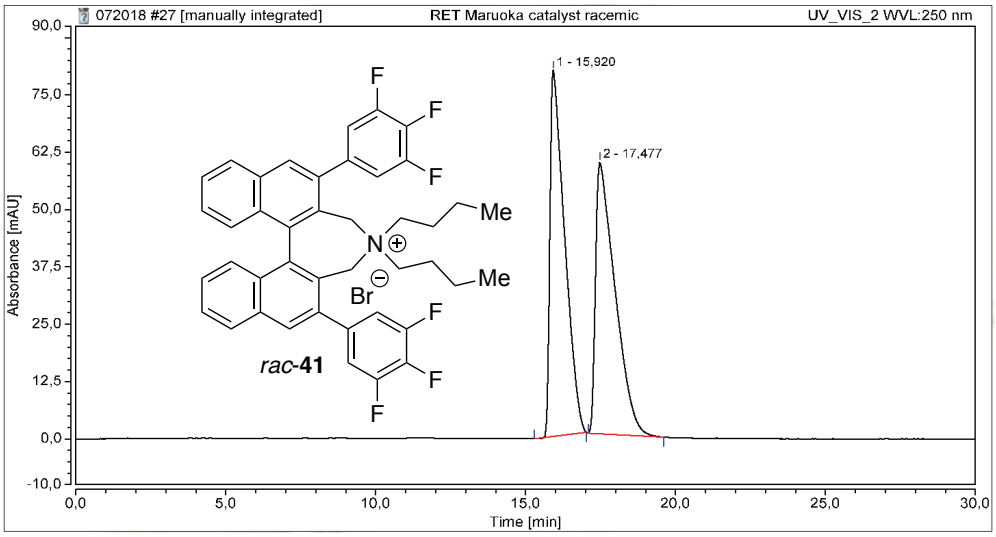


No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	5.47	n.a.	153.874	38.347	50.05
2	11.82	n.a.	96.187	38.267	49.95
Total:			250.061	76.614	100.00

6.26.1. (S_a)-41



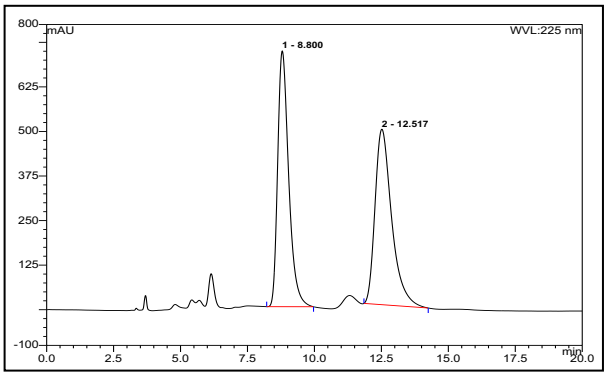
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount µl
n.a.	Pyrene	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		17,143	79,342	91,848	100,00	100,00	n.a.
Total:			**79,342**	**91,848**	**100,00**	**100,00**	

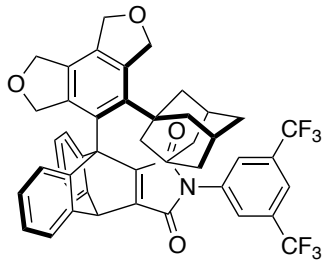


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount µl
n.a.	Pyrene	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1		15,920	45,189	79,882	50,30	57,38	n.a.
2		17,477	44,644	59,332	49,70	42,62	n.a.
Total:			**89,833**	**139,213**	**100,00**	**100,00**	

6.26.2. Rotational Profile of (*ap*)-56e

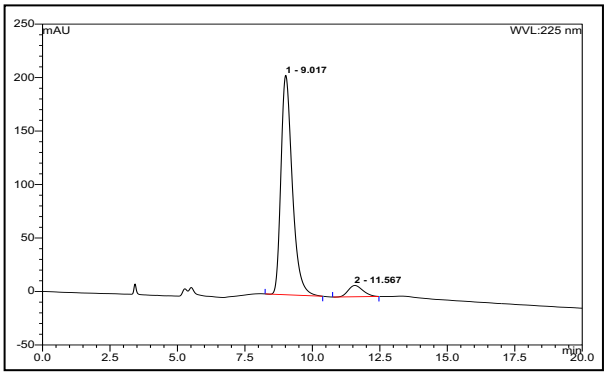
6.26.2.1. (±*ap*)-56e

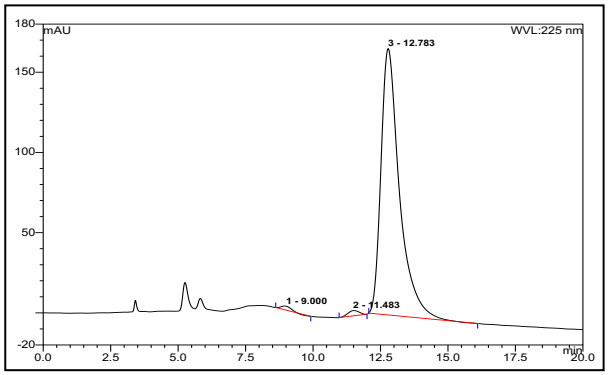




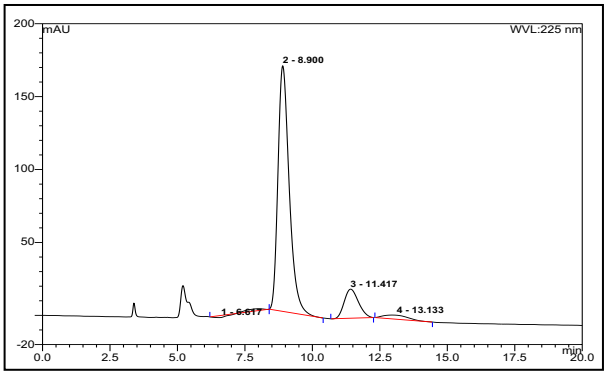
(*ap*)-**56e**

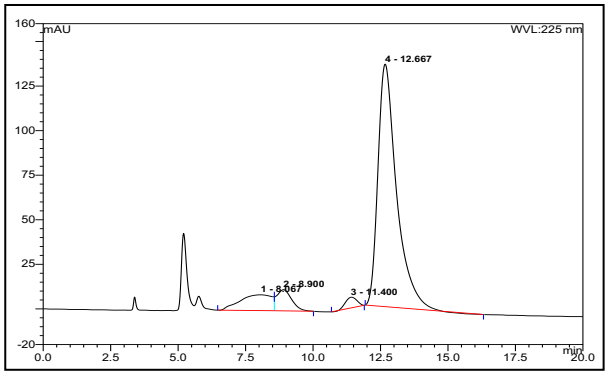
6.26.2.2. Start



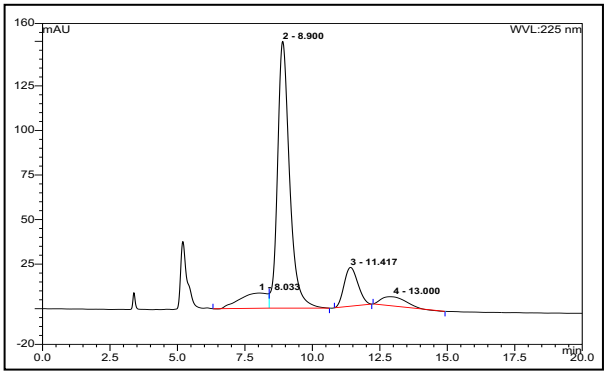


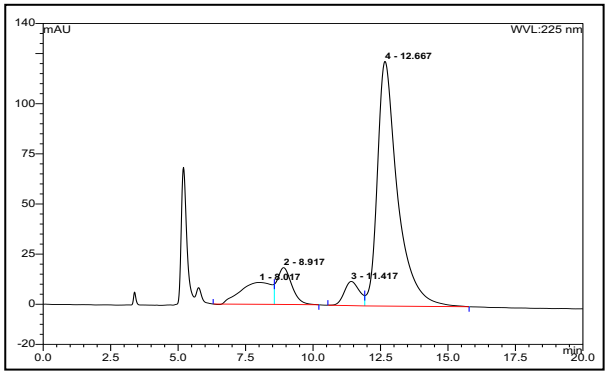
6.26.2.3. 2 Hours



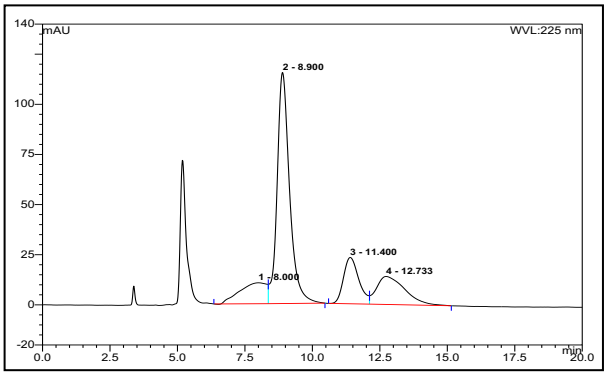


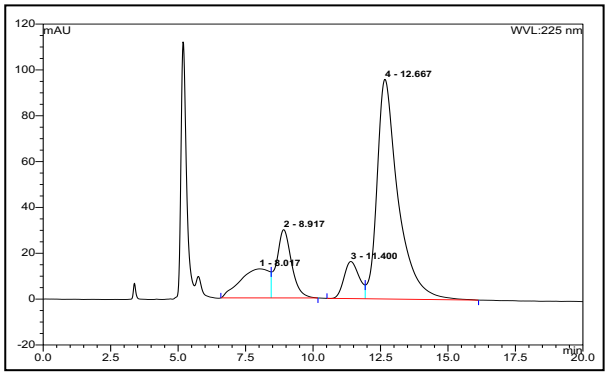
6.26.2.4. 4 Hours



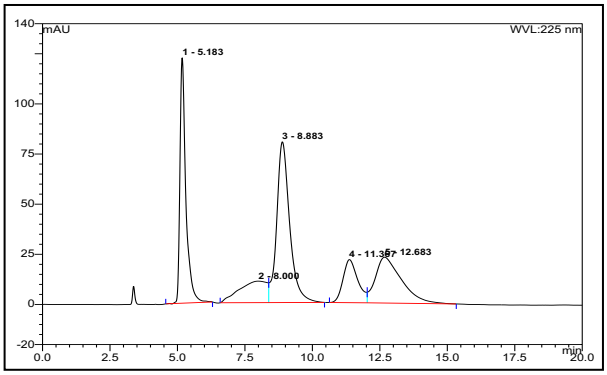


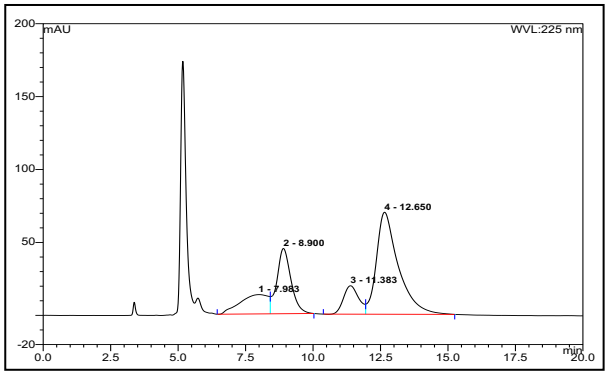
6.26.2.5. 8 Hours





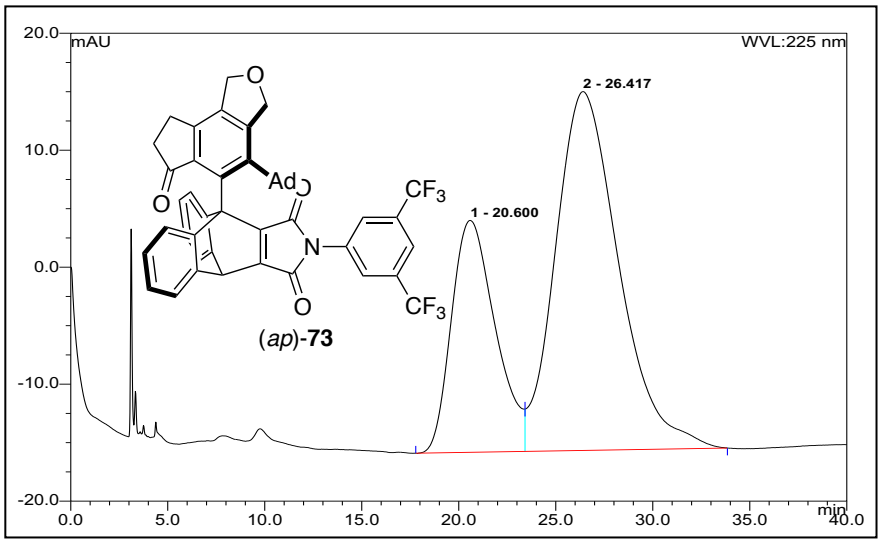
6.26.2.6. 16 Hours



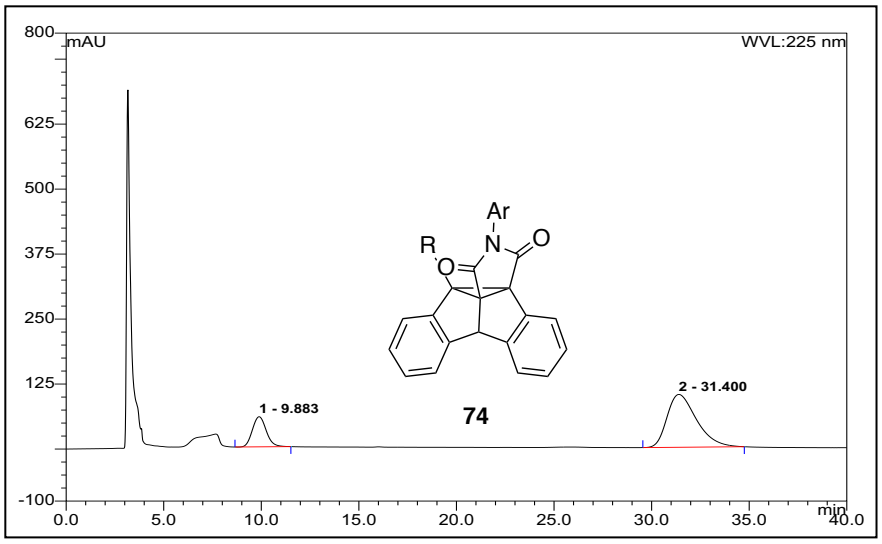


6.26.3. Di-π–methane Rearrangement

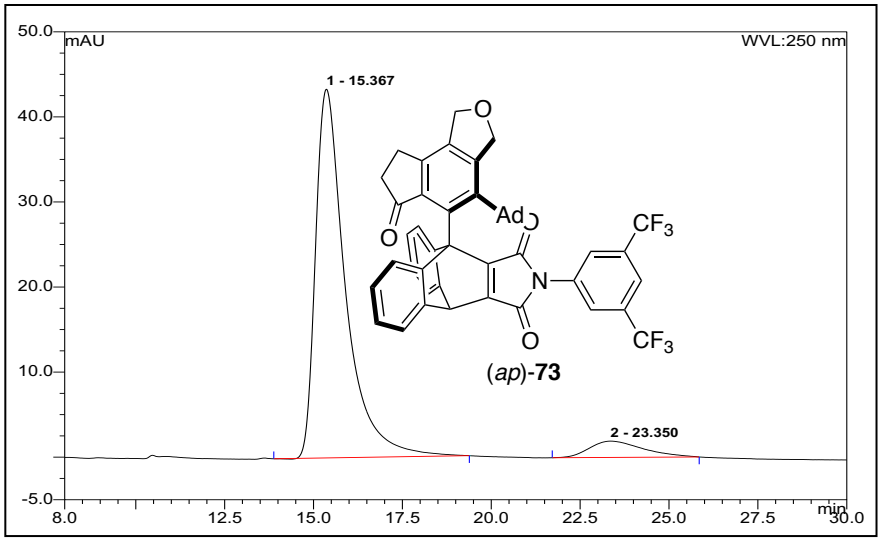
6.26.3.1. (*ap*)-73



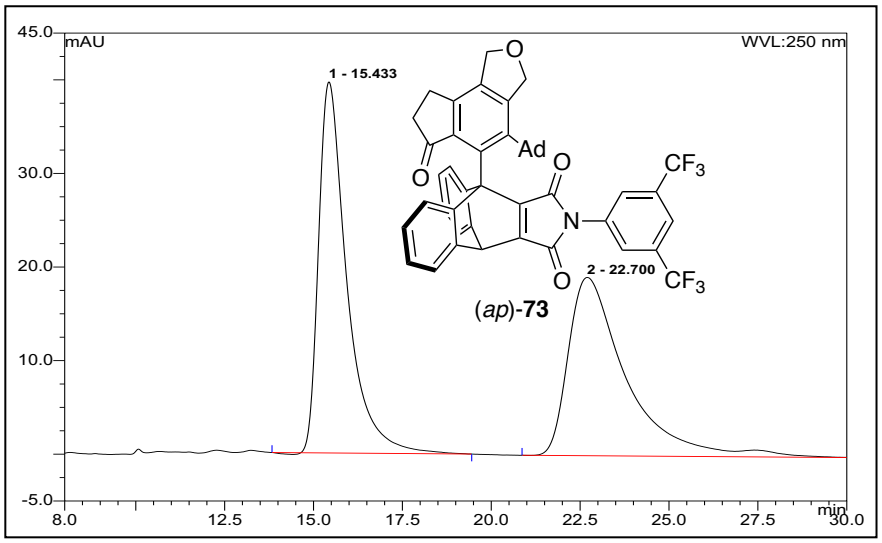
6.26.3.2. 74



6.26.4. (*ap*)-73



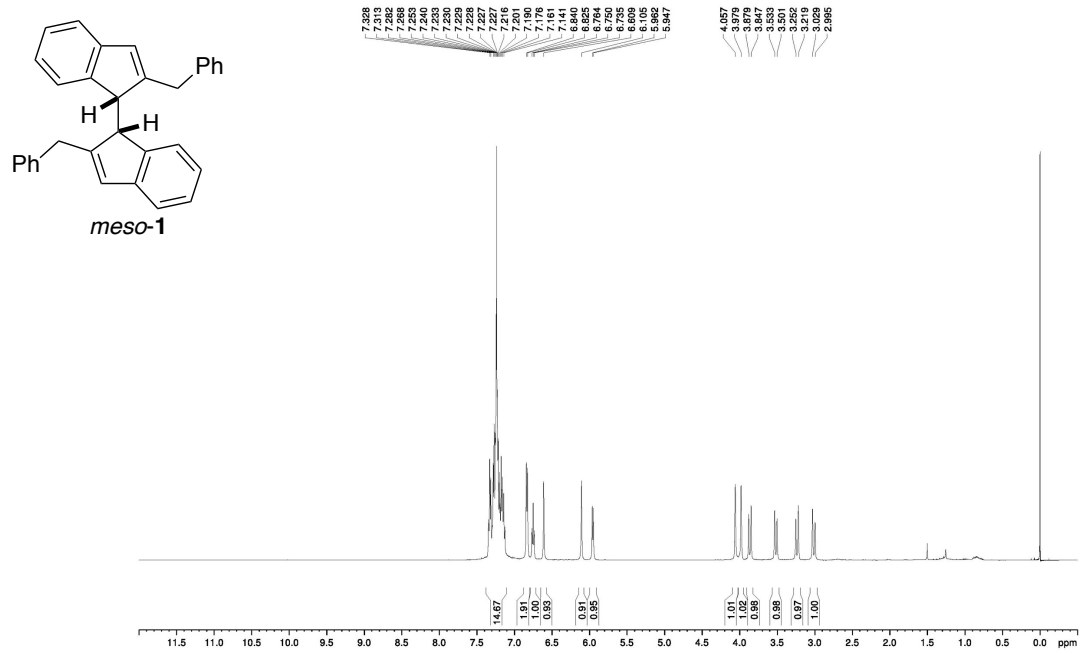
No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	15.37	n.a.	43.343	42.344	92.68
2	23.35	n.a.	1.918	3.343	7.32
Total:			45.261	45.687	100.00



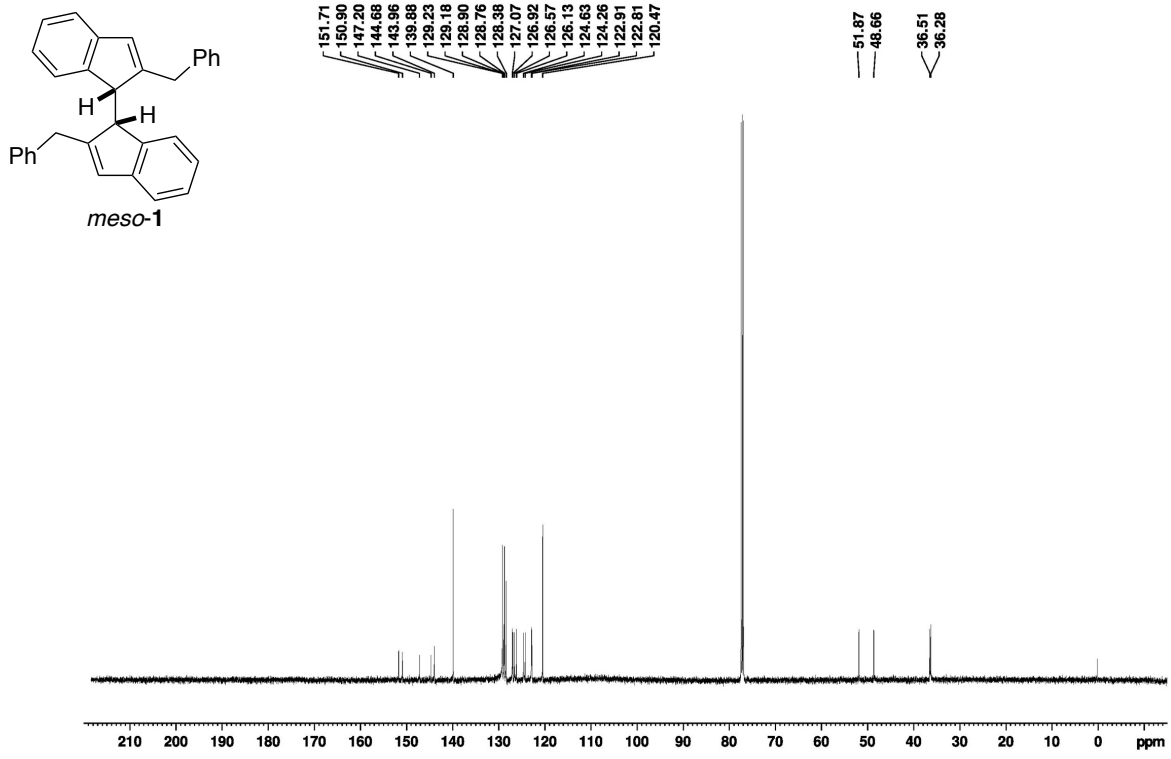
No.	Ret.Time [min]	Peak Name	Height [mAU]	Area [mAU*min]	Rel.Area [%]
1	15.43	n.a.	39.654	36.472	50.34
2	22.70	n.a.	19.047	35.979	49.66
Total:			58.702	72.451	100.00

6.27. NMR Spectra

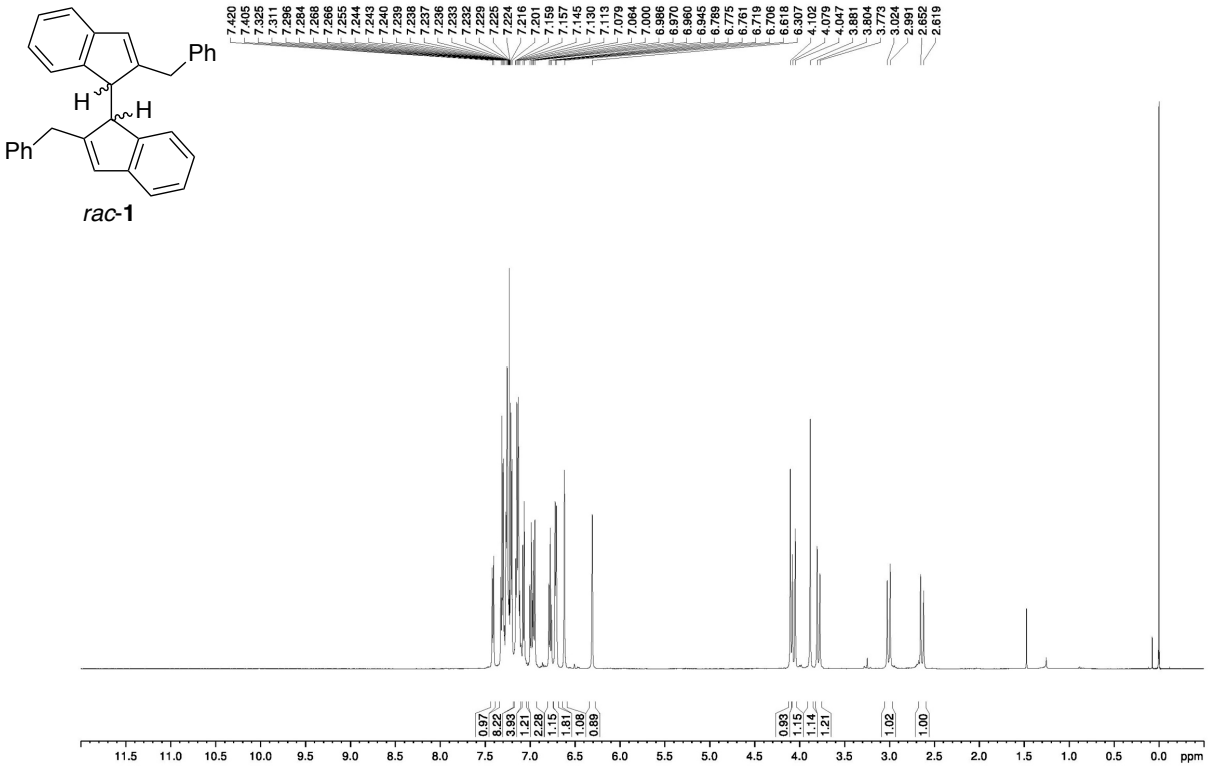
meso-**1**, ^{1}H NMR (500 MHz, $CDCl_3$, as a 1:1 mixture of rotamers)



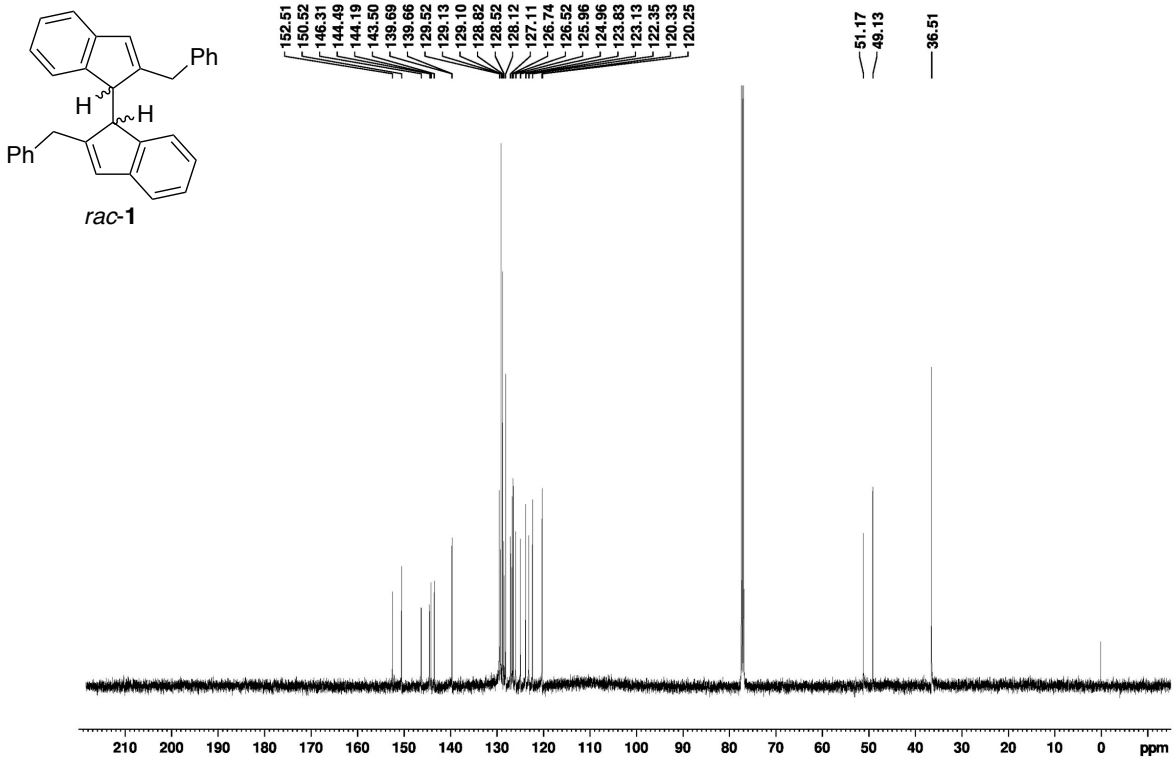
meso-**1**, ^{13}C NMR (126 MHz, $CDCl_3$)



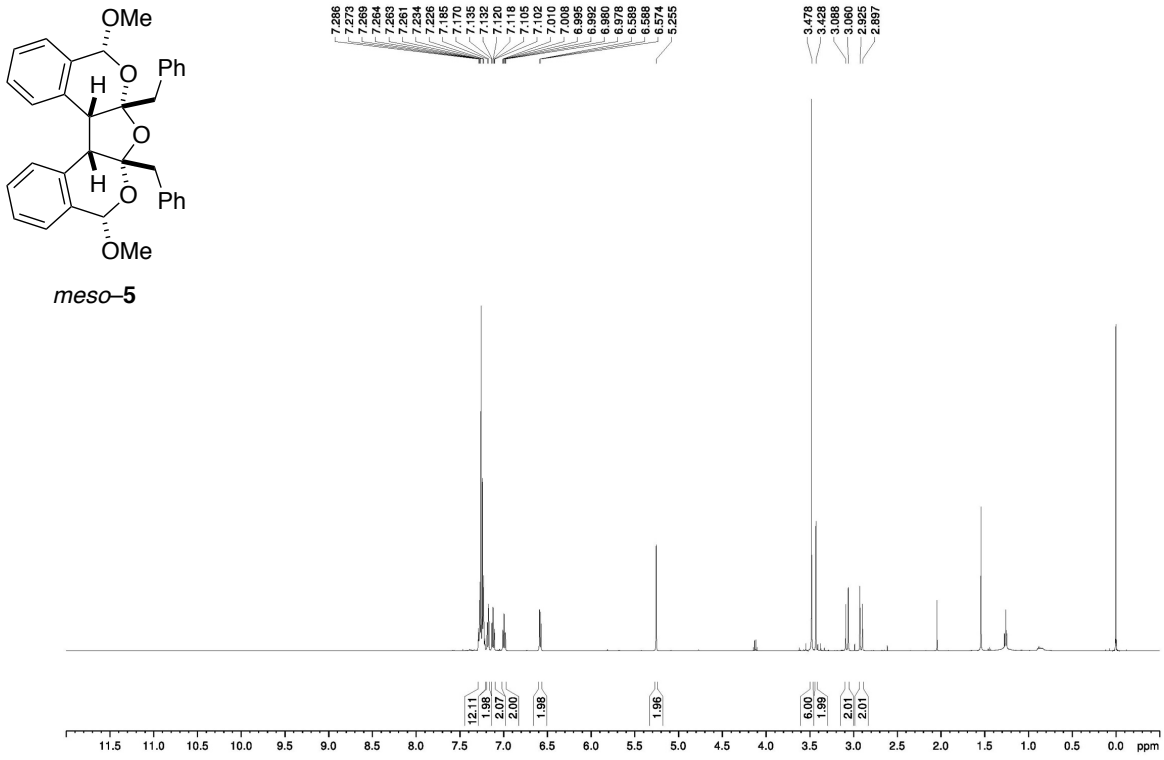
rac-**1**, ^{1}H NMR (500 MHz, $CDCl_3$, as a 1:1 mixture of rotamers)



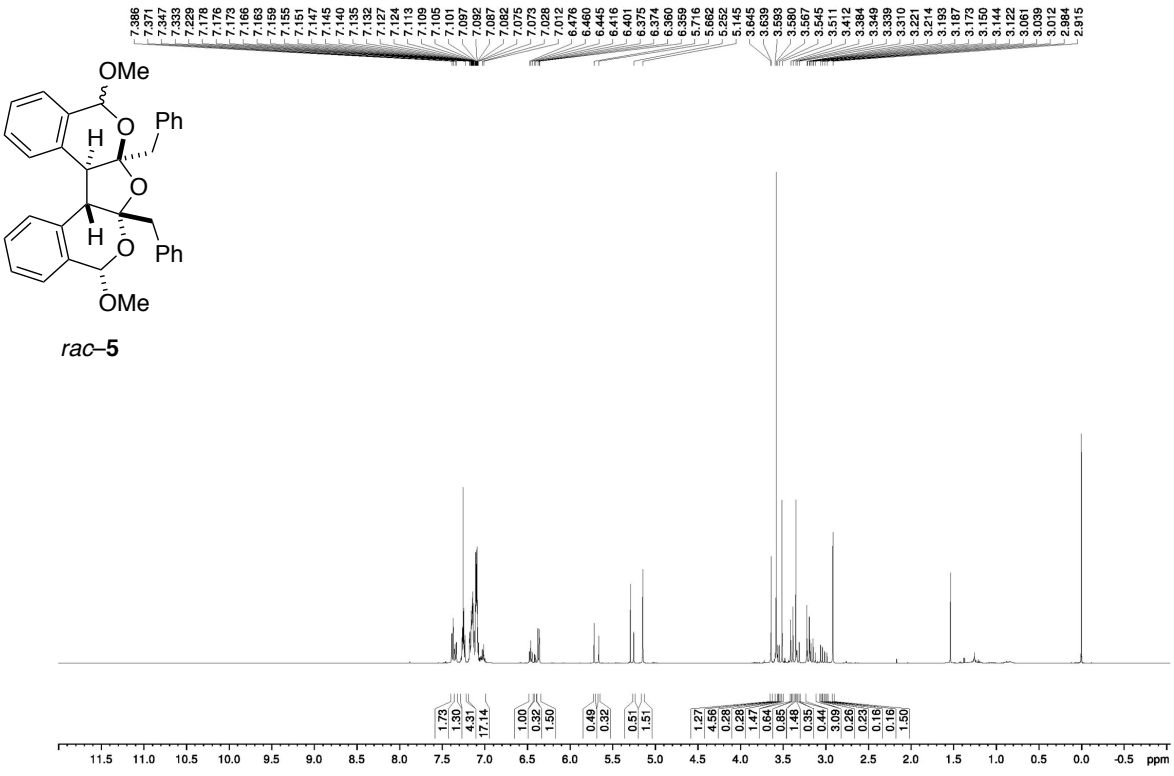
rac-**1**, ^{13}C NMR (126 MHz, $CDCl_3$)



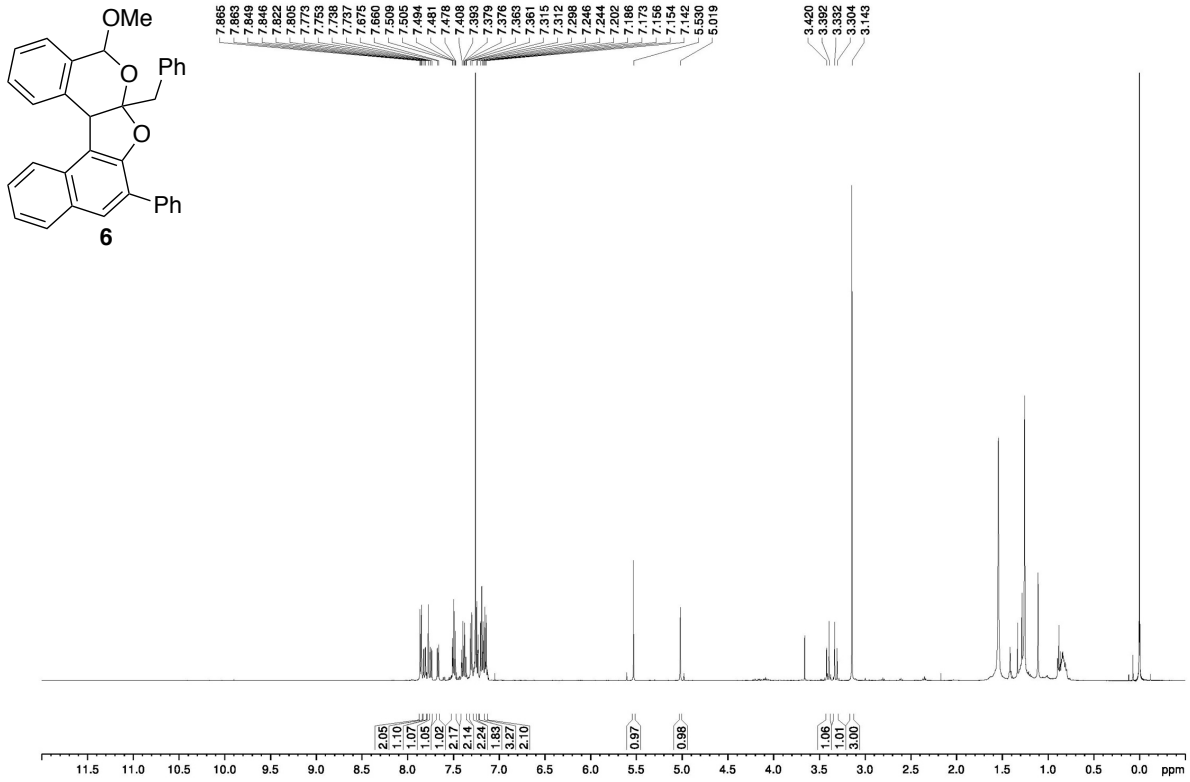
meso-**5**, ^{1}H NMR (500 MHz, $CDCl_3$)



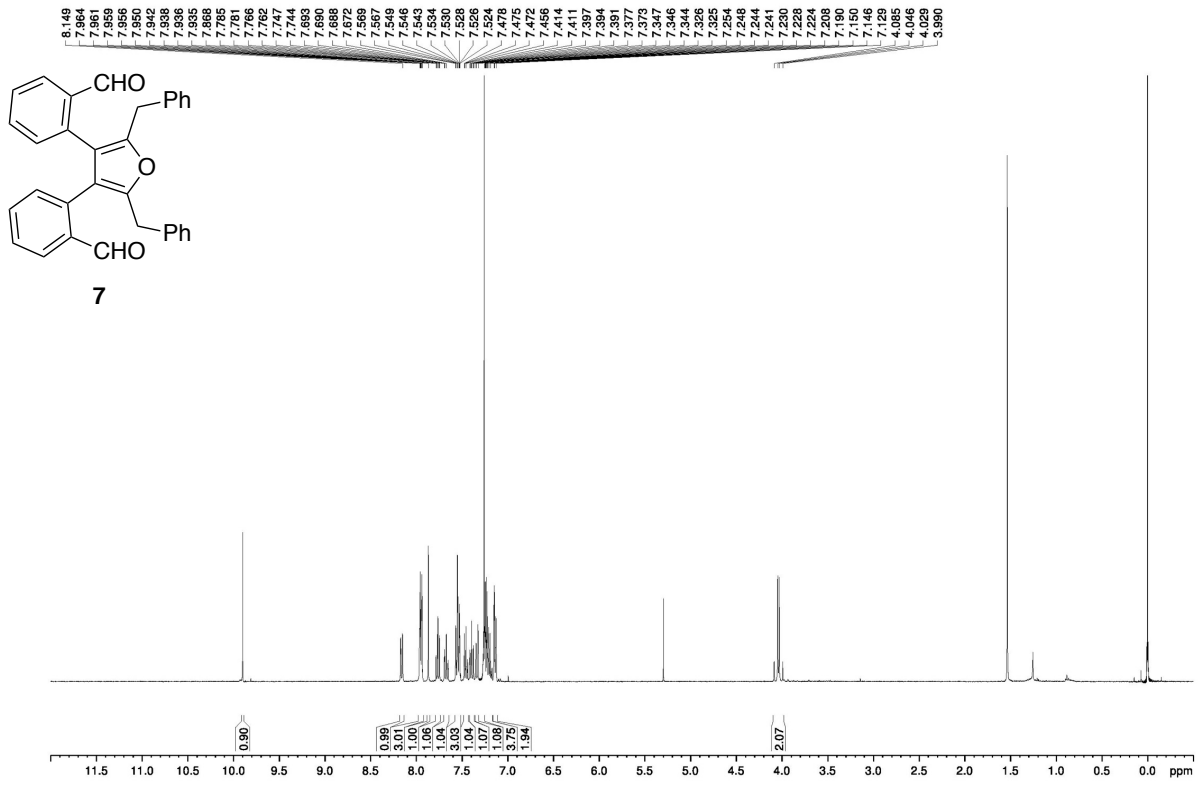
rac-**5**, ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoiosmers)



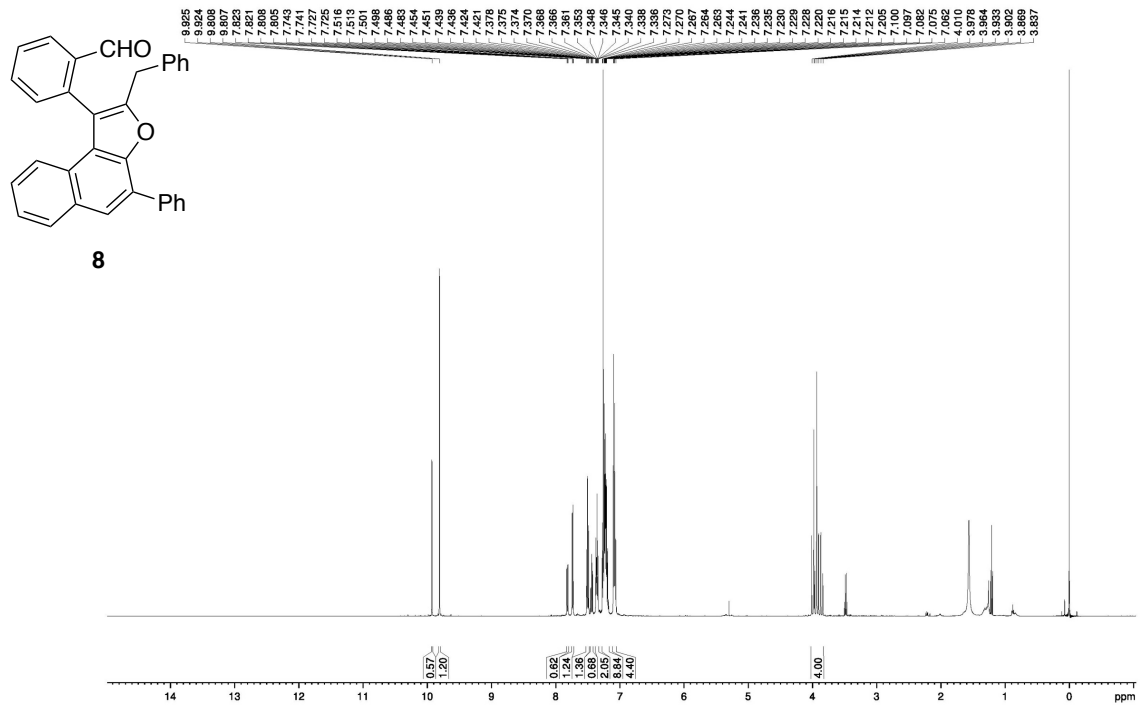
6, ^{1}H NMR (500 MHz, $CDCl_3$)



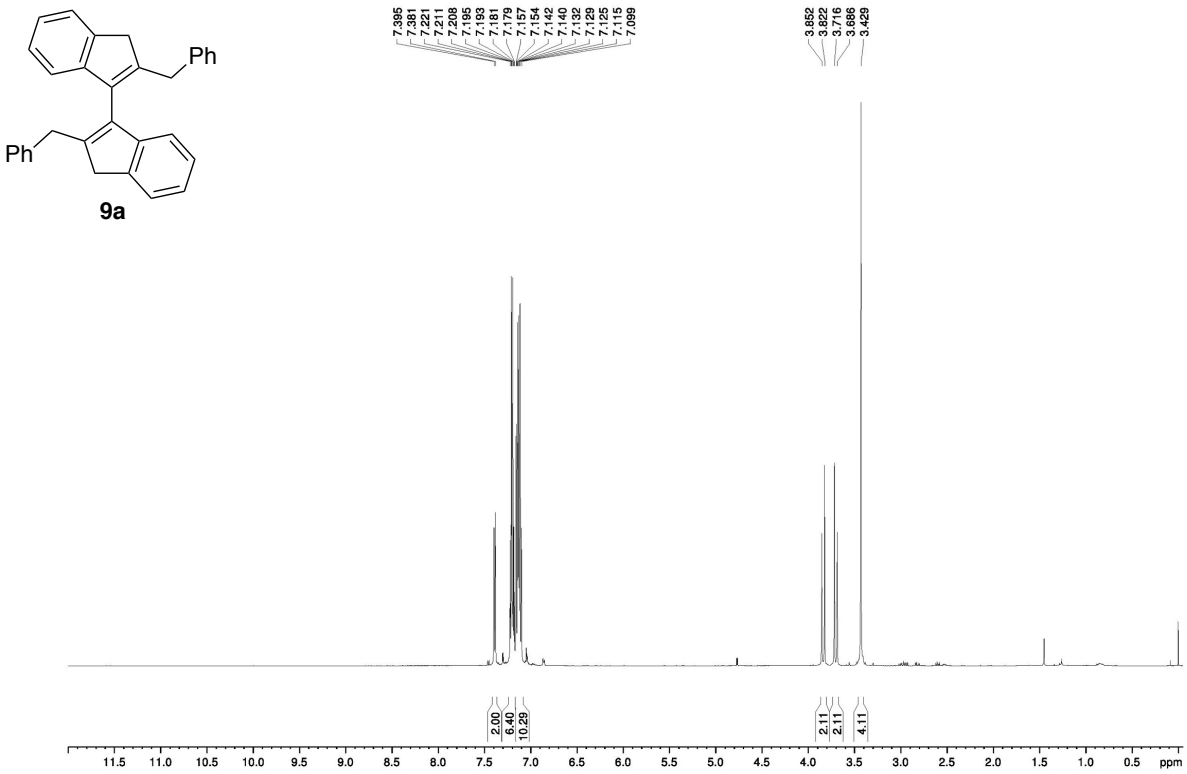
7, ^{1}H NMR (400 MHz, $CDCl_3$)



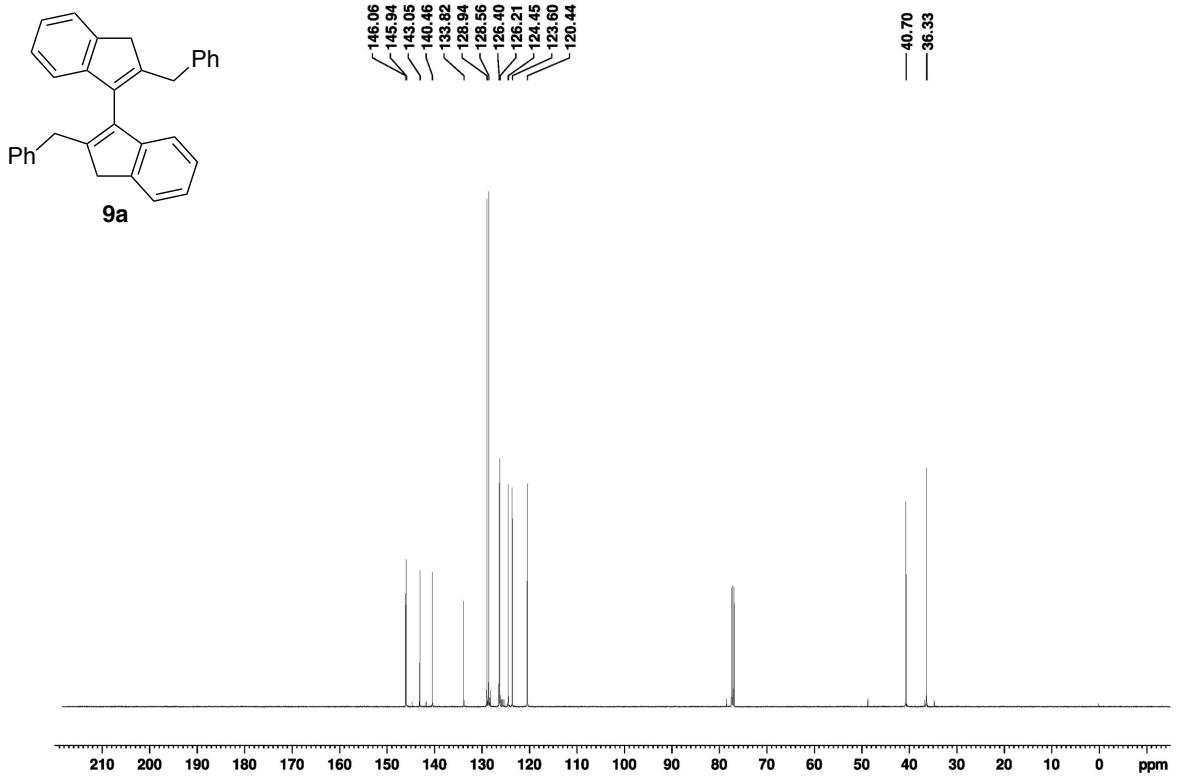
8, ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers)



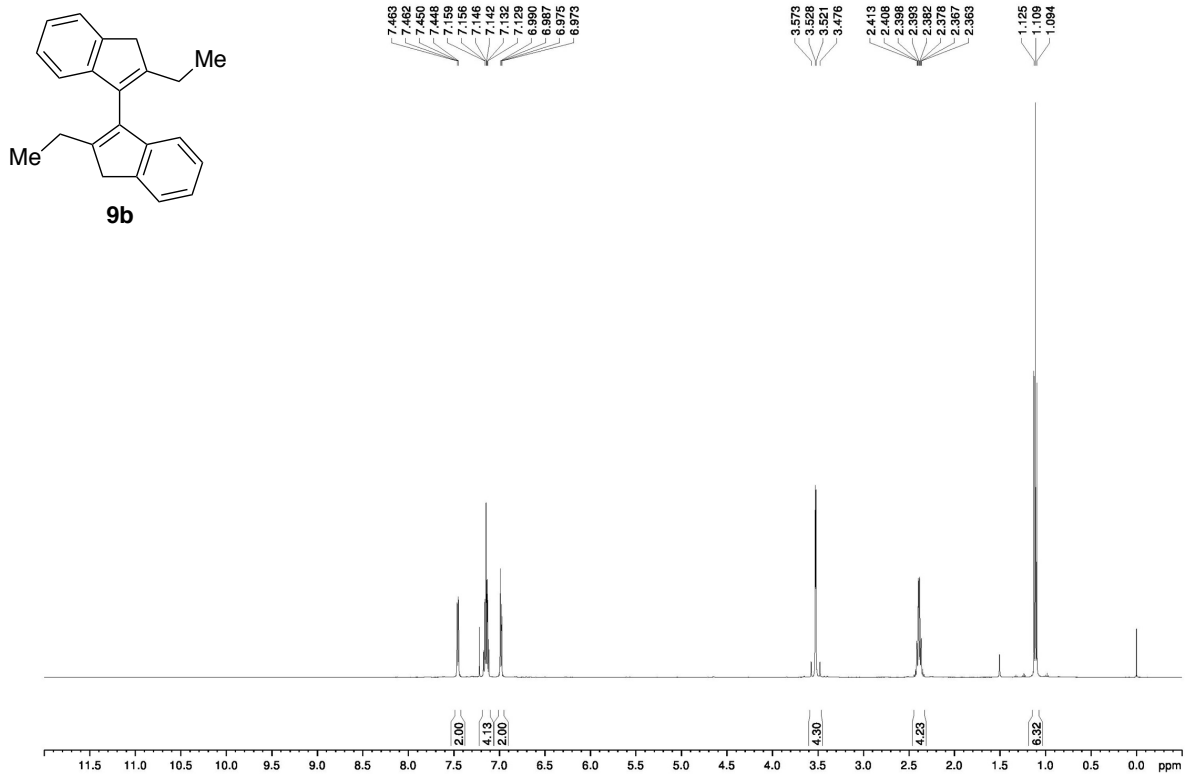
9a, ^{1}H NMR (500 MHz, $CDCl_3$)



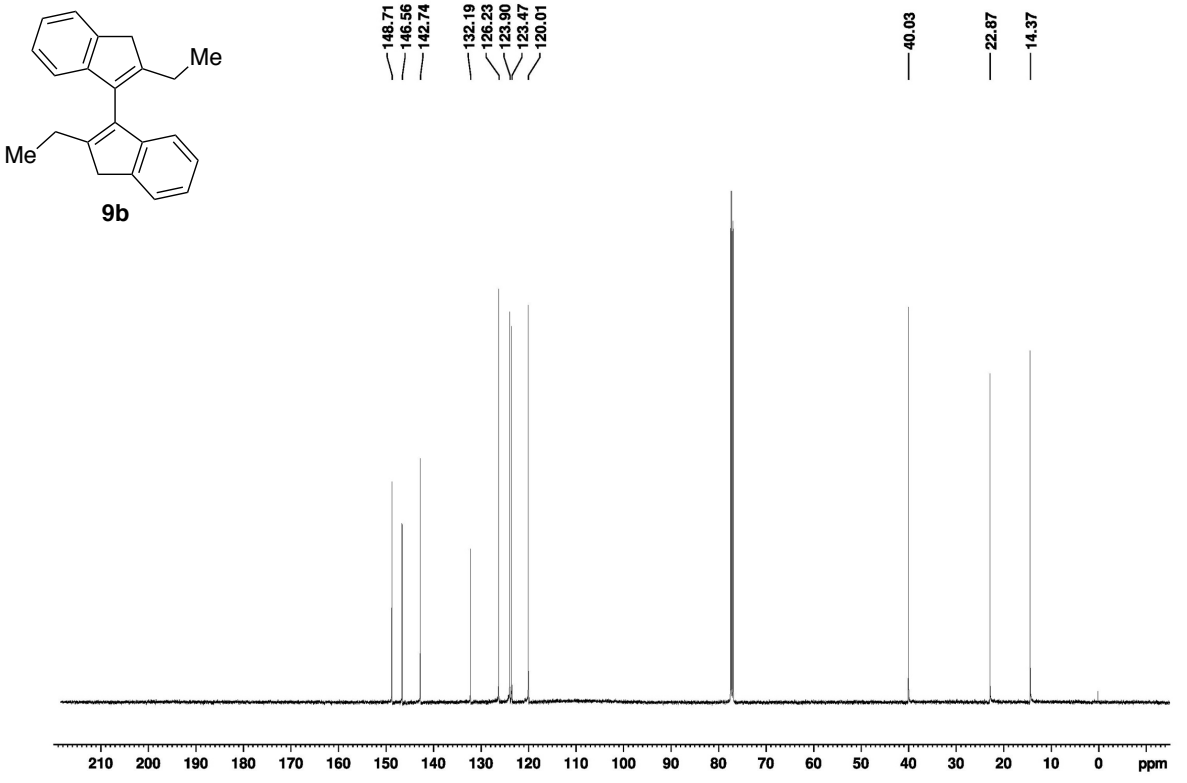
9a,^{13}C NMR (126 MHz, $CDCl_3$)



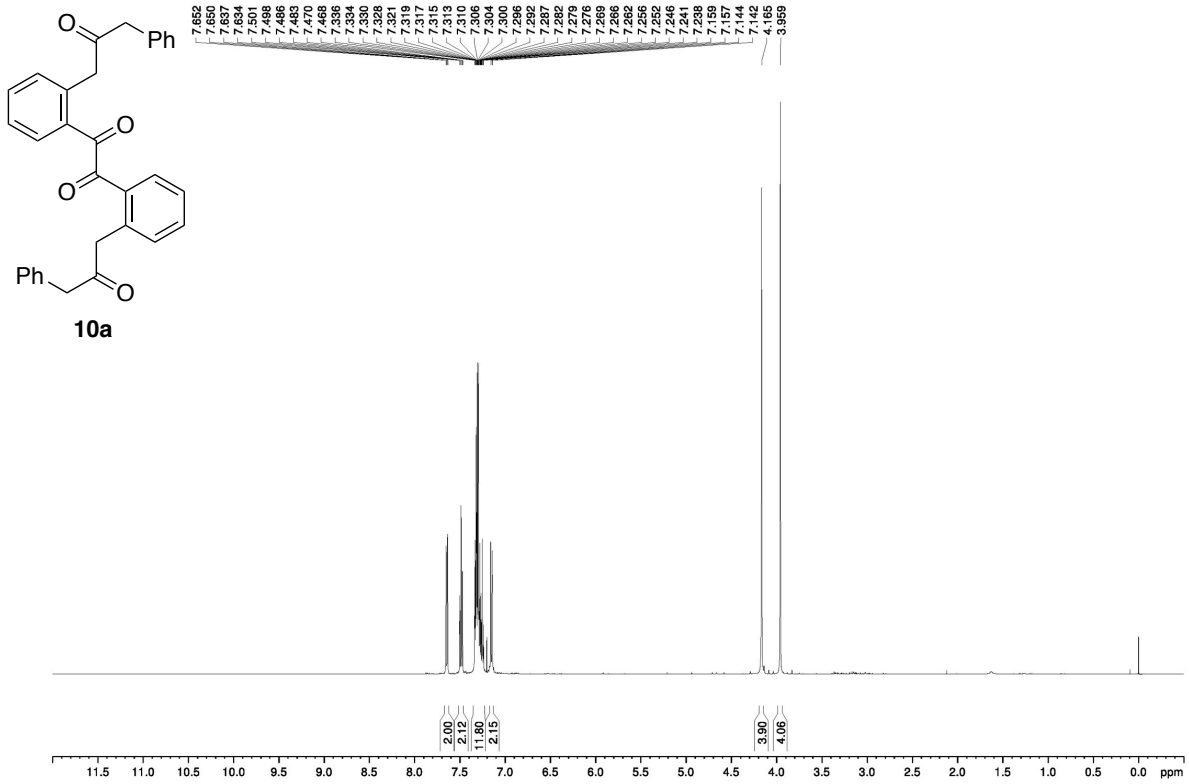
9b, ^{1}H NMR (500 MHz, $CDCl_3$)



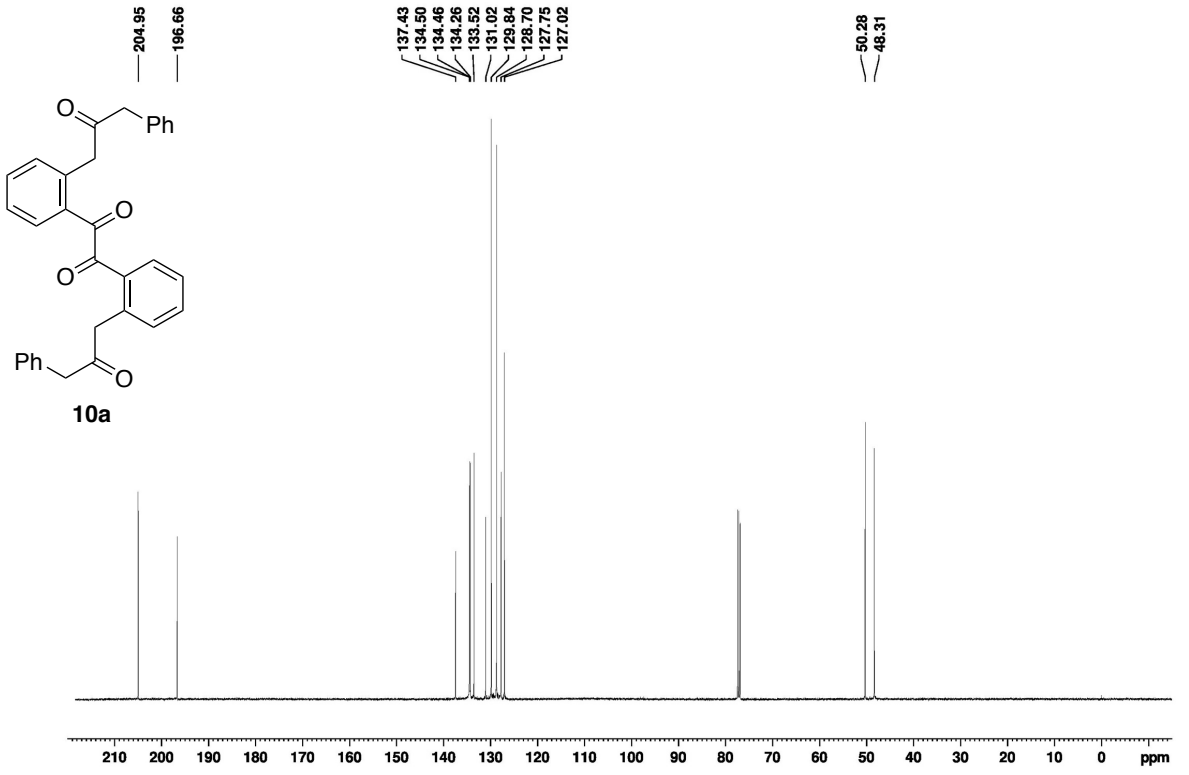
9b,^{13}C NMR (126 MHz, $CDCl_3$)



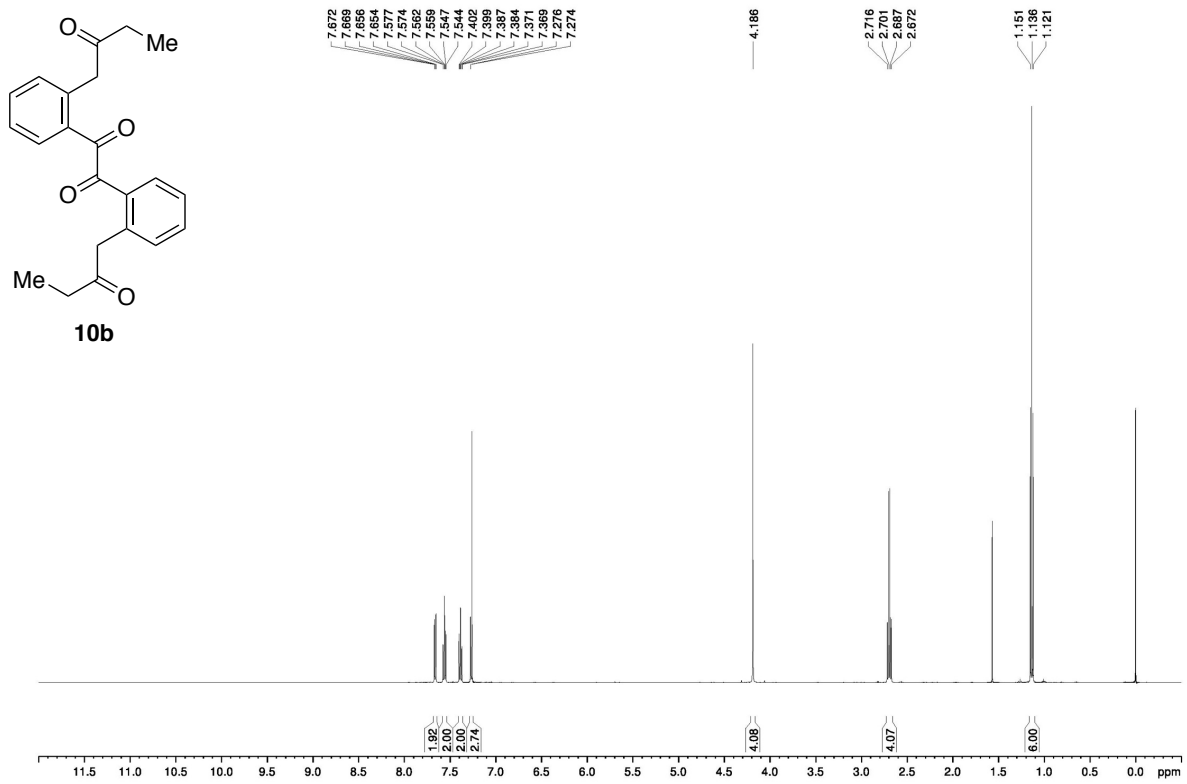
10a, ^{1}H NMR (500 MHz, $CDCl_3$)



10a,^{13}C NMR (126 MHz, $CDCl_3$)

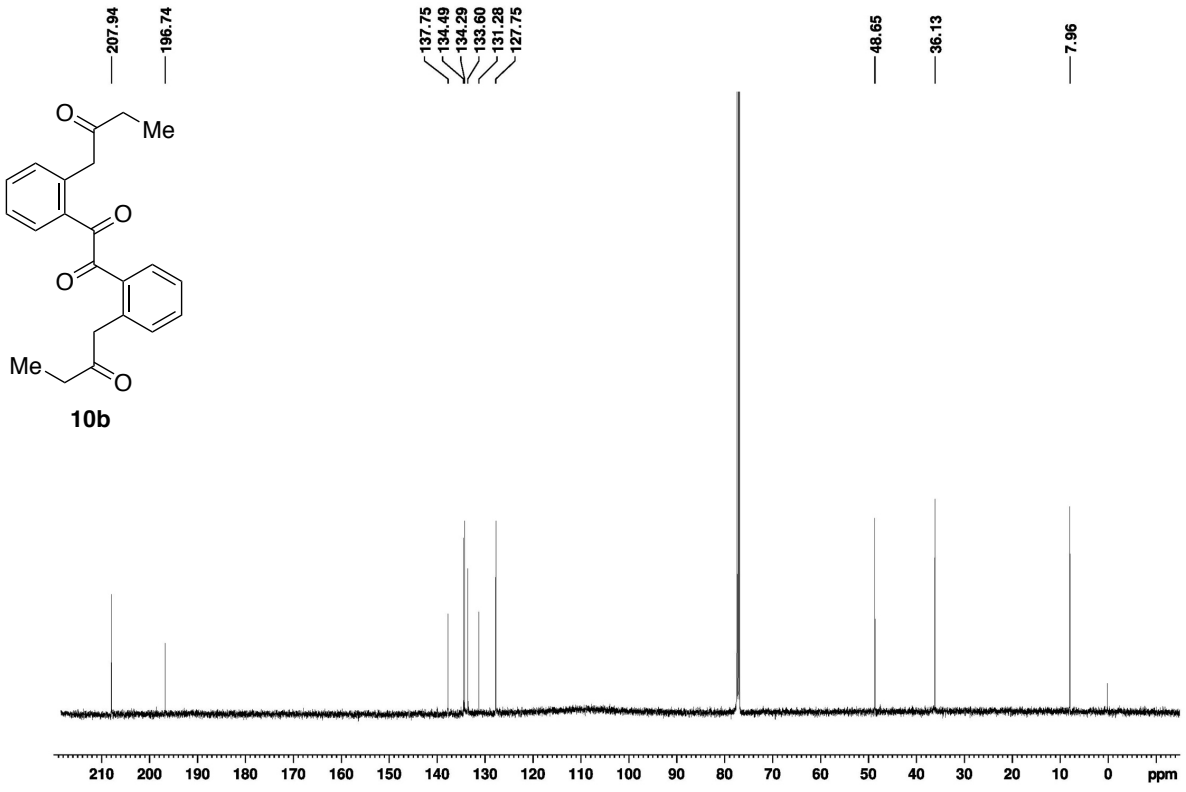


10b, ^{1}H NMR (500 MHz, $CDCl_3$)



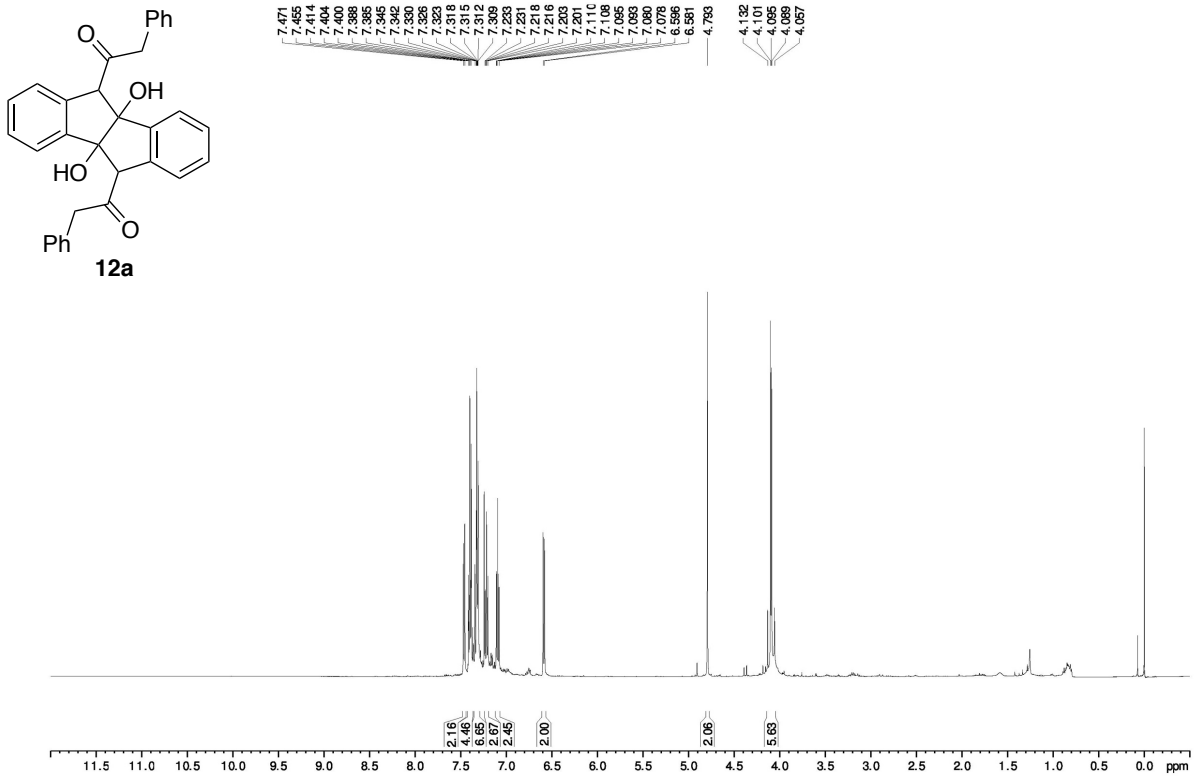
10b

10b, ^{13}C NMR (126 MHz, $CDCl_3$)

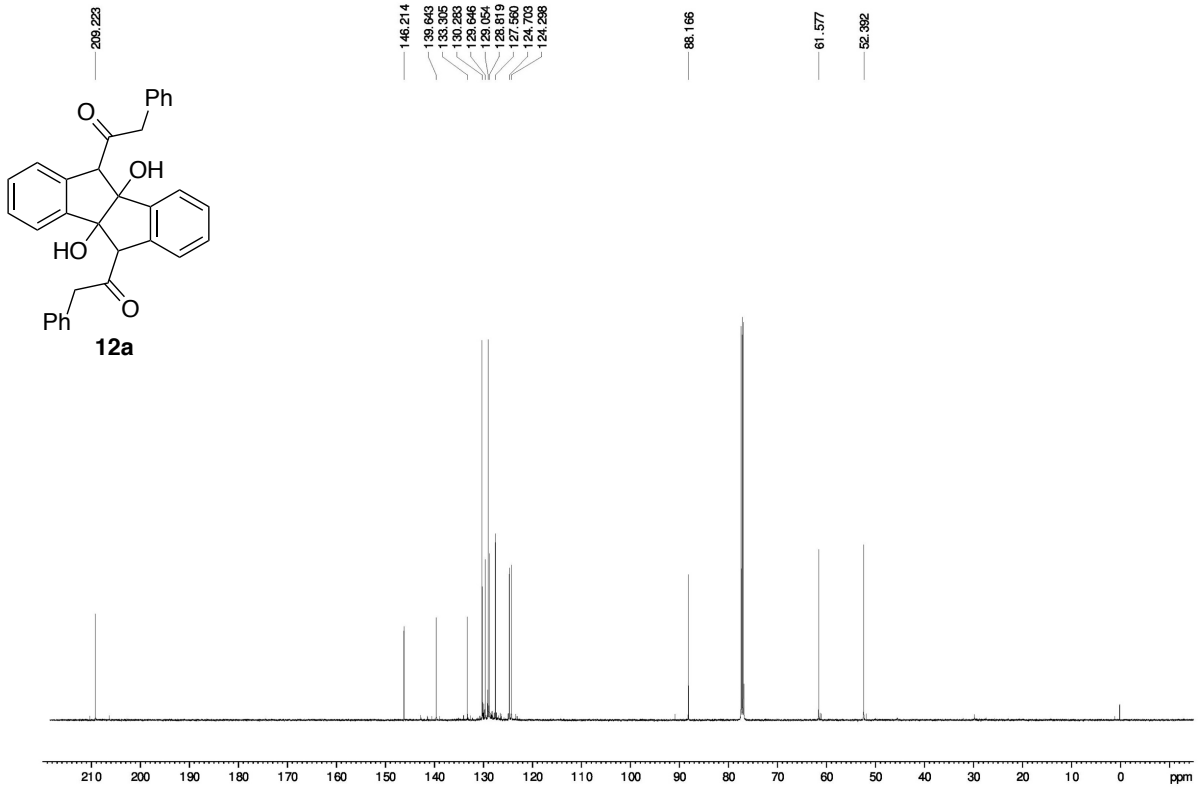


10b

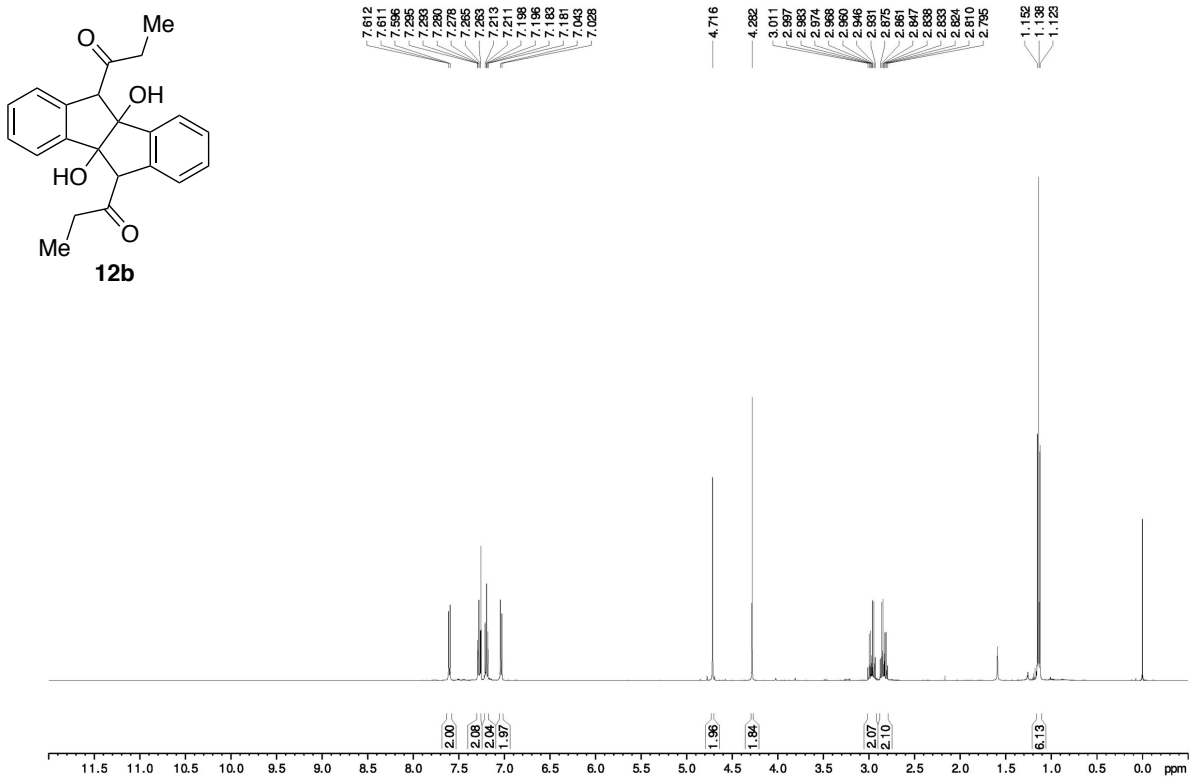
12a, ^{1}H NMR (500 MHz, $CDCl_3$)



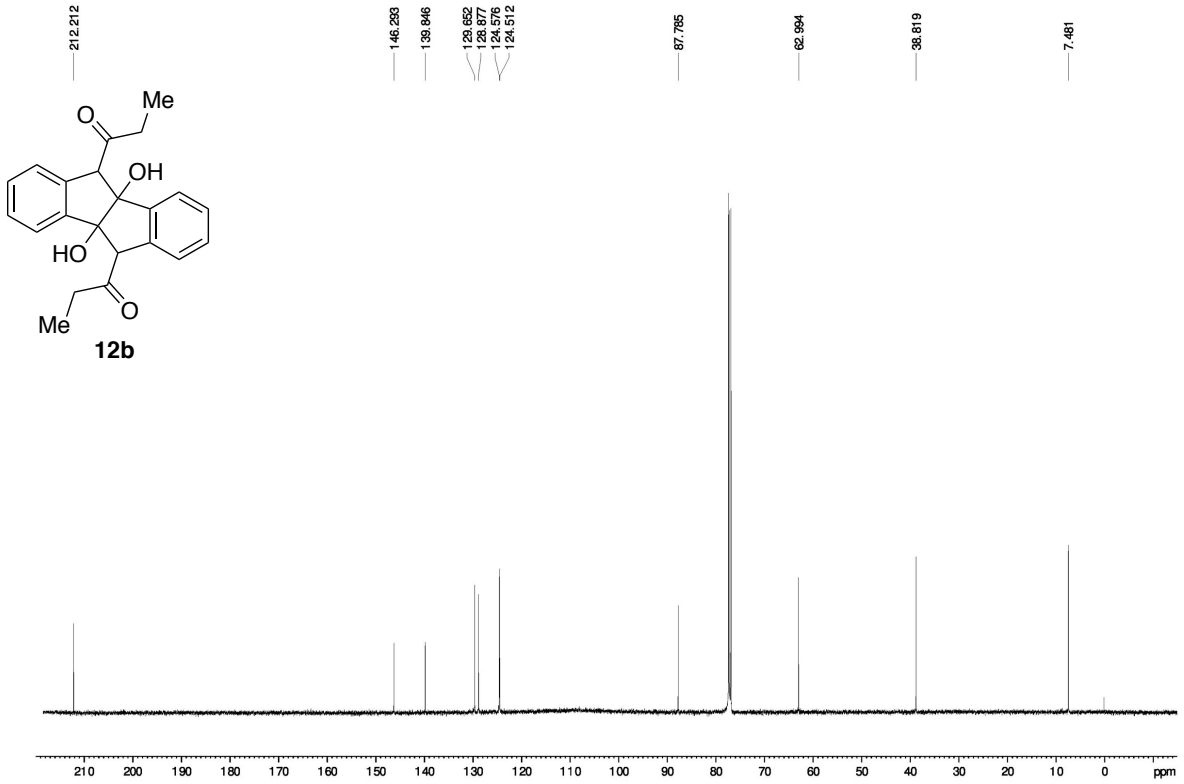
12a, ^{13}C NMR (126 MHz, $CDCl_3$)



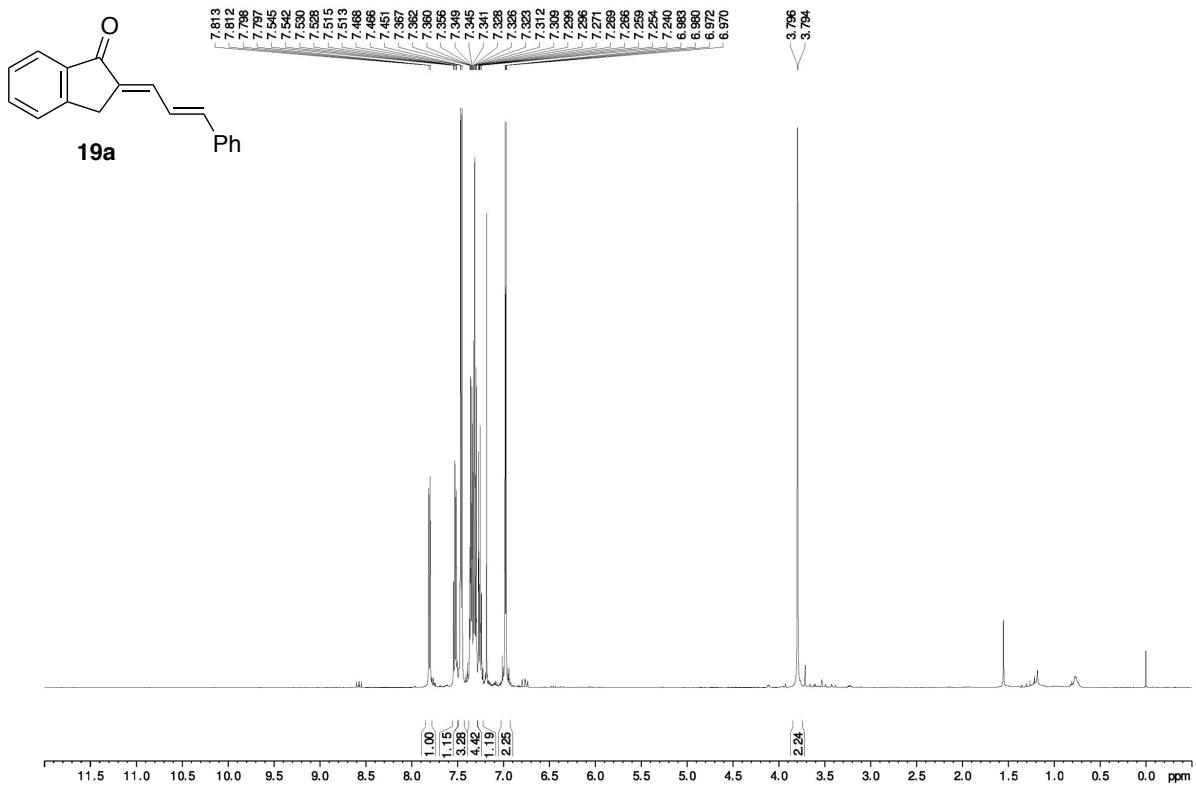
12b, ^{1}H NMR (500 MHz, $CDCl_3$)



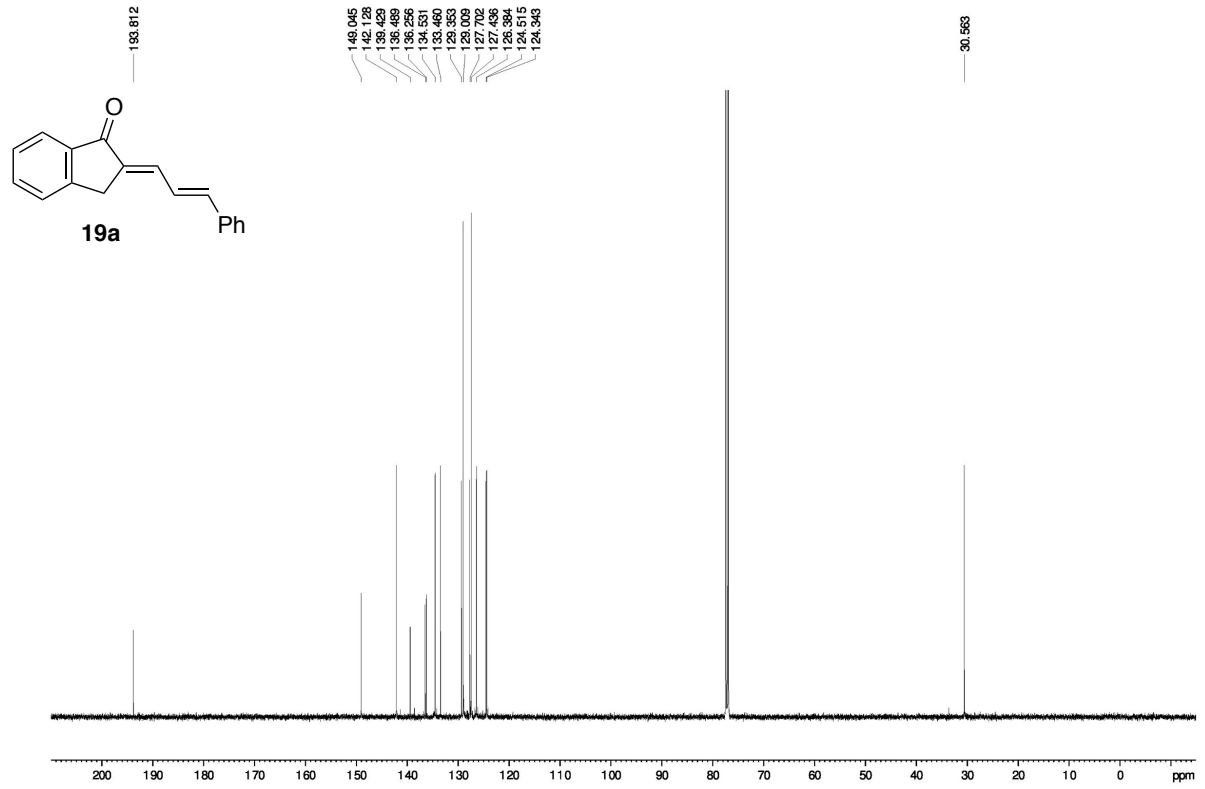
12b,^{13}C NMR (126 MHz, $CDCl_3$)



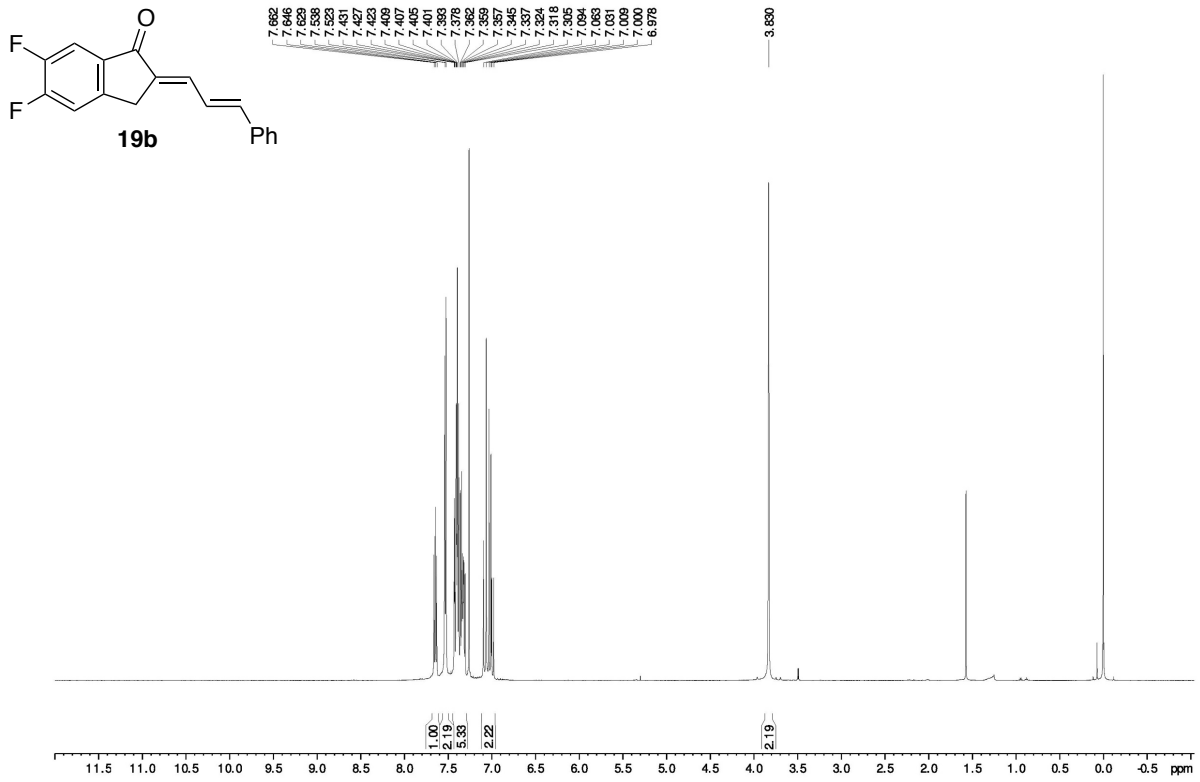
19a, ^{1}H NMR (500 MHz, $CDCl_3$)



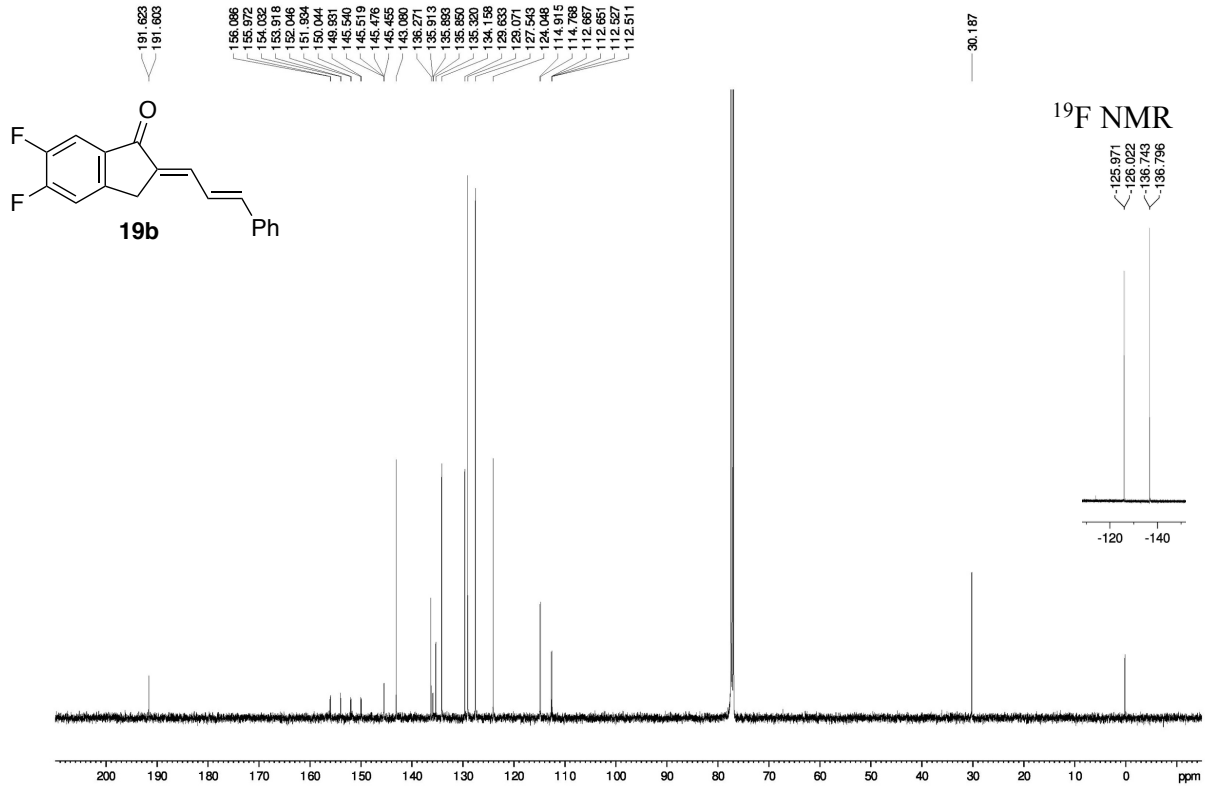
19a,^{13}C NMR (126 MHz, $CDCl_3$)



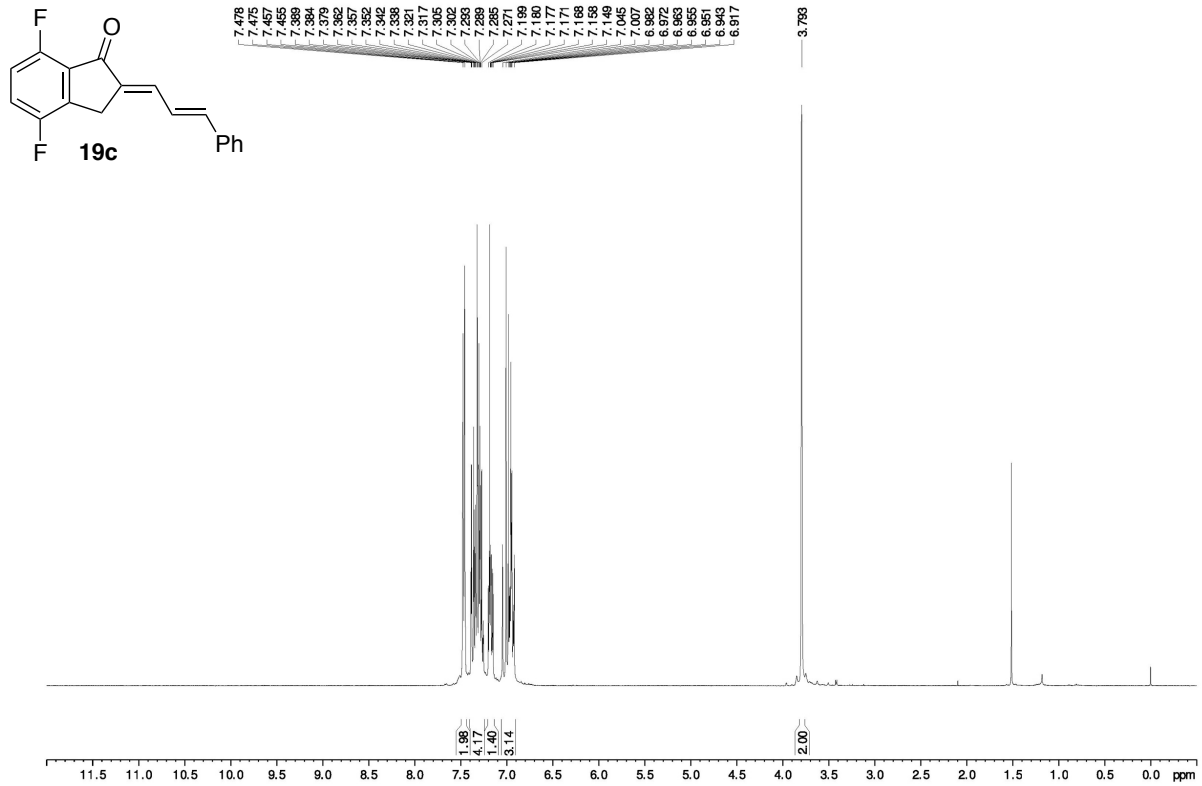
19b, ^{1}H NMR (500 MHz, $CDCl_3$)



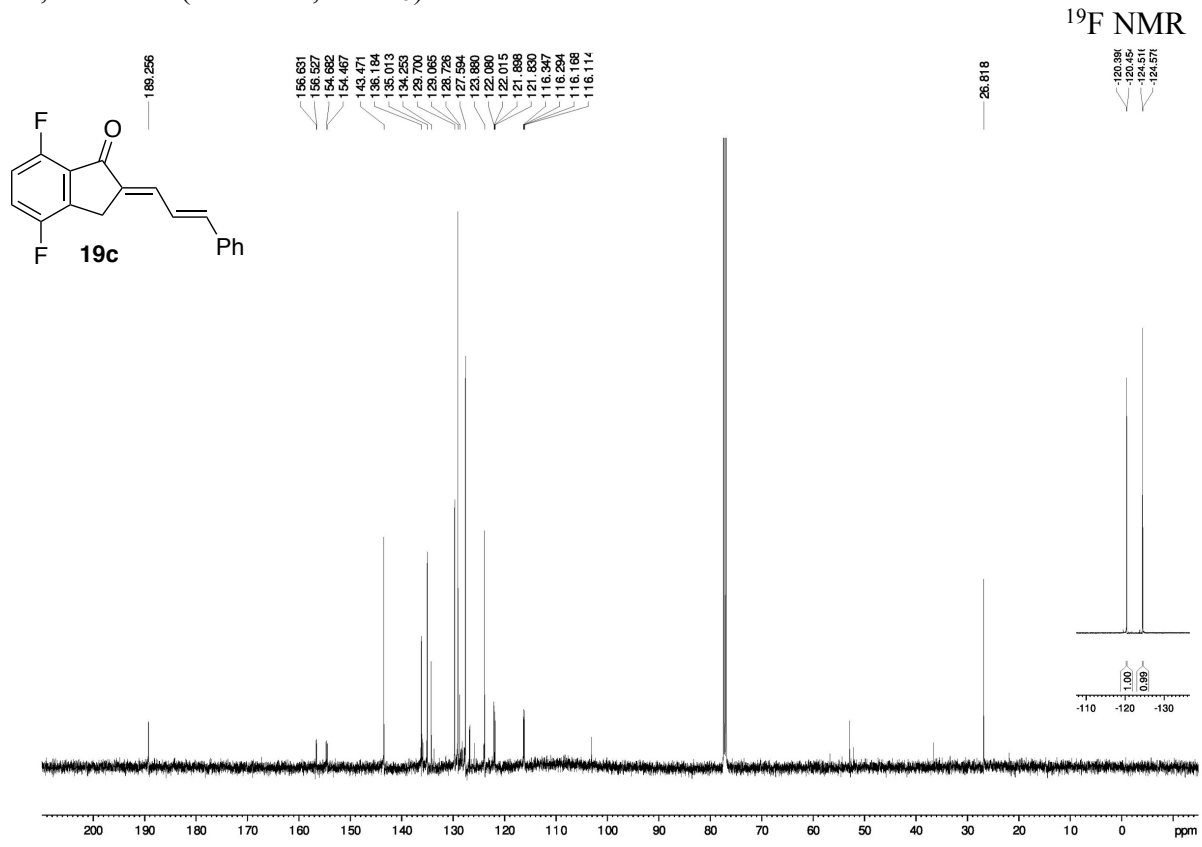
19b,^{13}C NMR (126 MHz, $CDCl_3$)



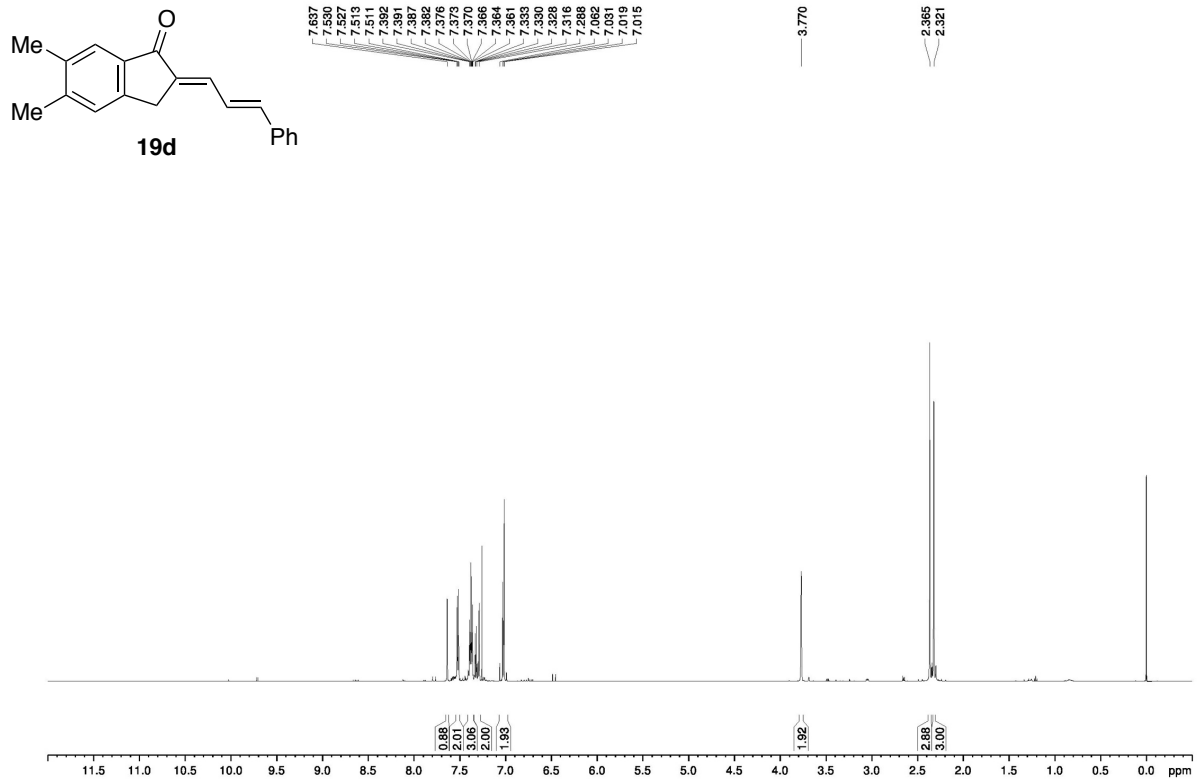
19c, ^{1}H NMR (400 MHz, $CDCl_3$)



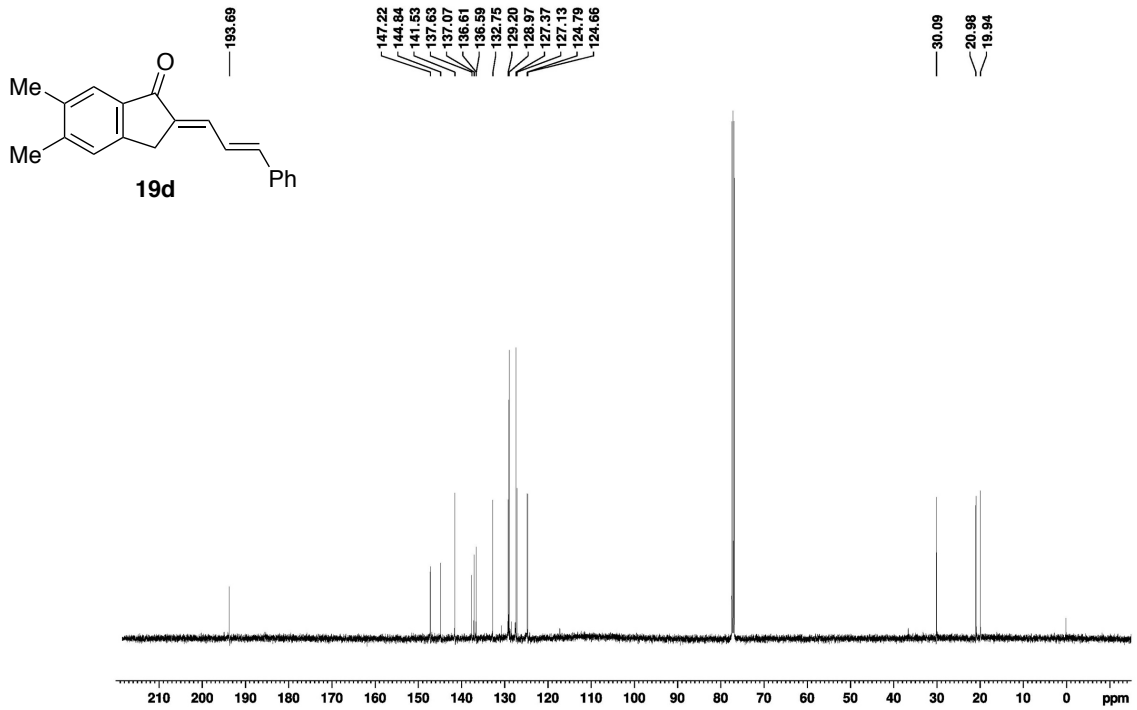
19c,^{13}C NMR (126 MHz, $CDCl_3$)



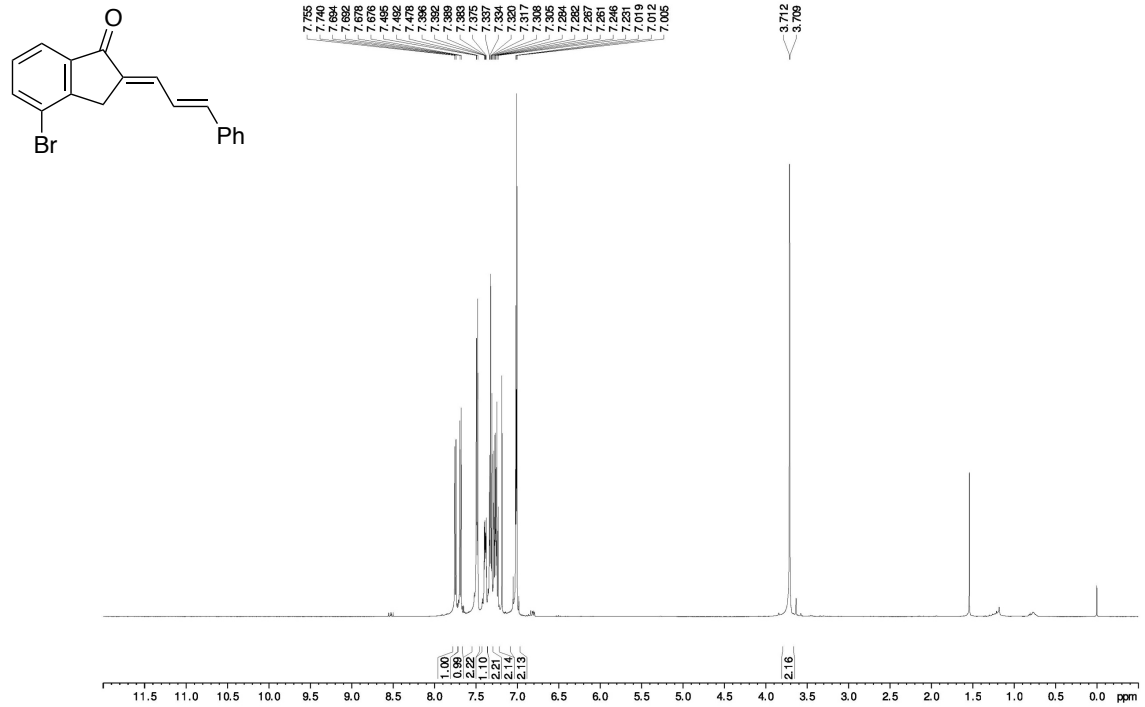
19d, ^{1}H NMR (500 MHz, $CDCl_3$)



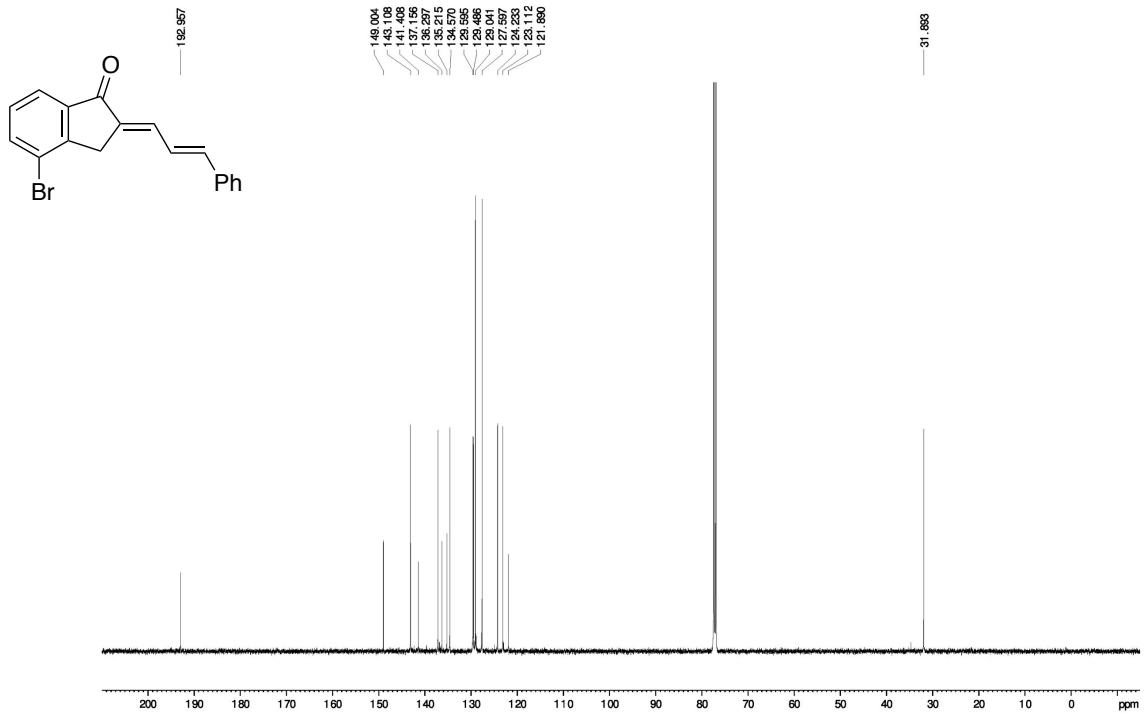
19d,^{13}C NMR (126 MHz, $CDCl_3$)



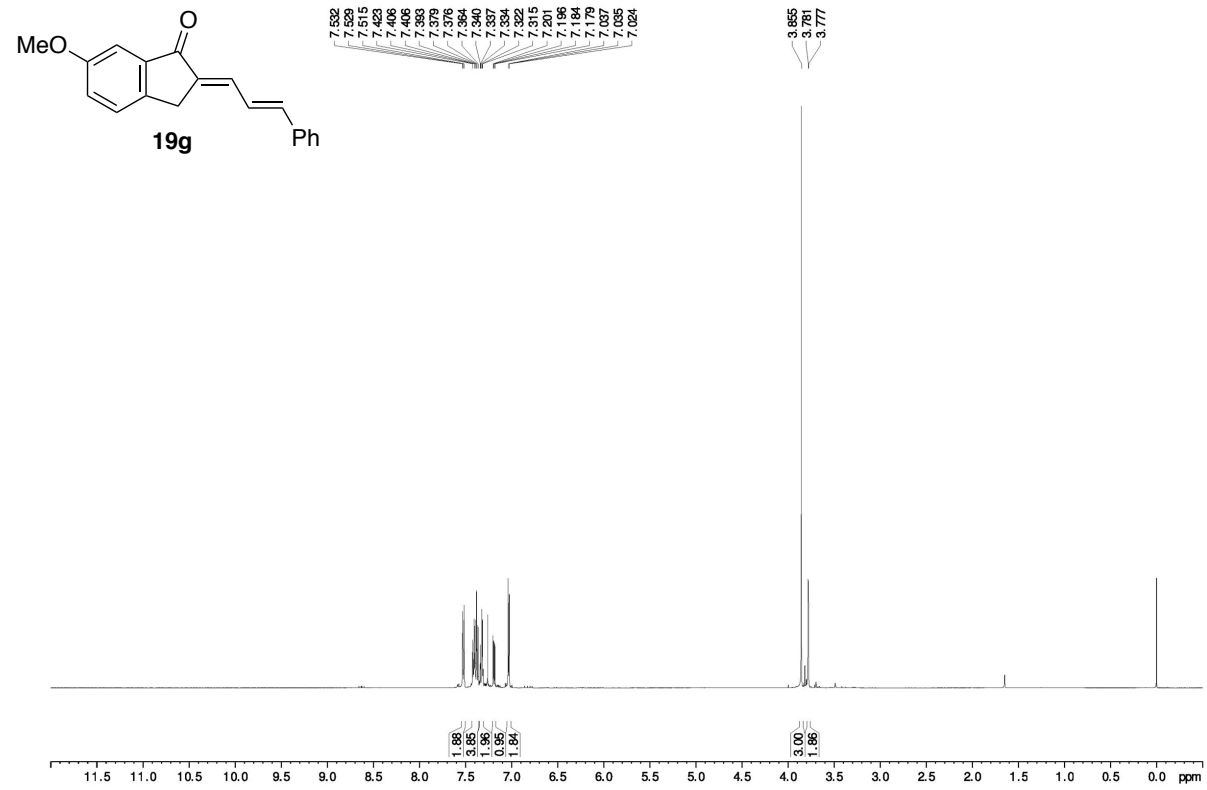
(*E*)-4-Bromo-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one, ^{1}H NMR (500 MHz, $CDCl_3$)



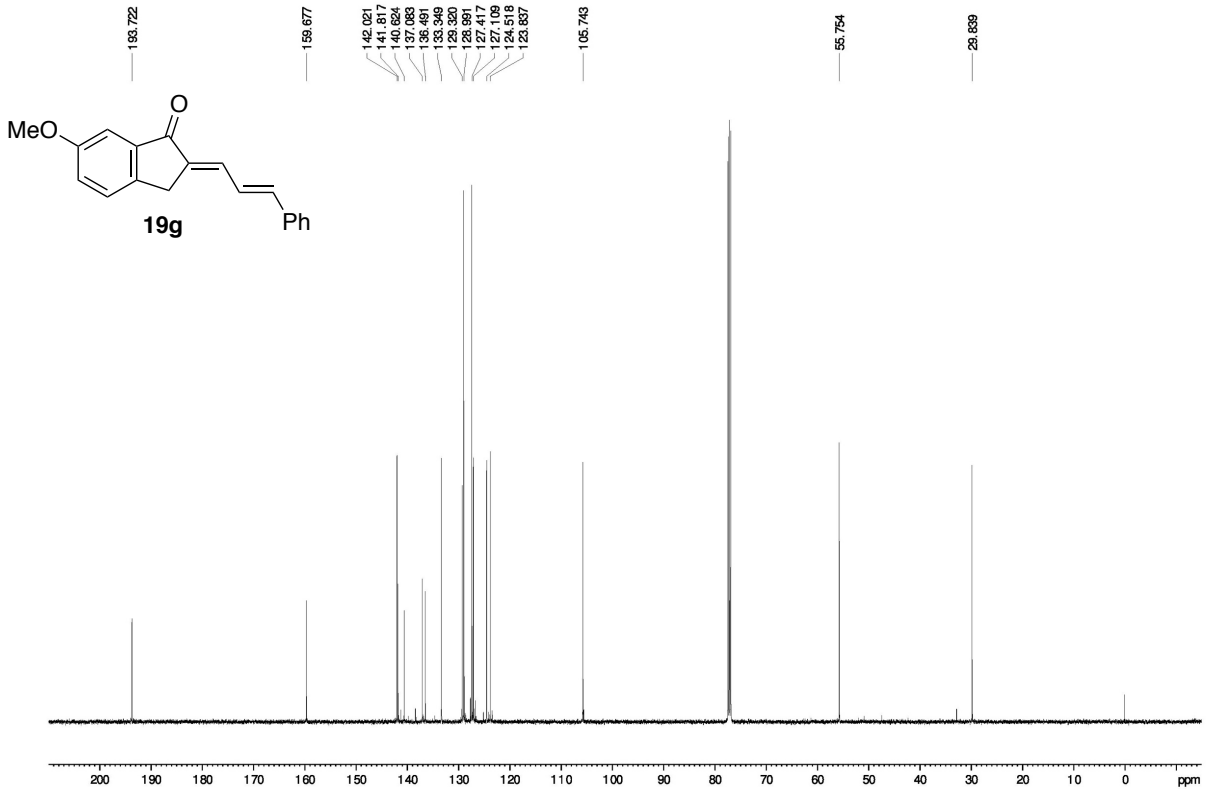
(*E*)-4-Bromo-2-((*E*)-3-phenylallylidene)-2,3-dihydro-1*H*-inden-1-one, ^{13}C NMR (126 MHz, $CDCl_3$)



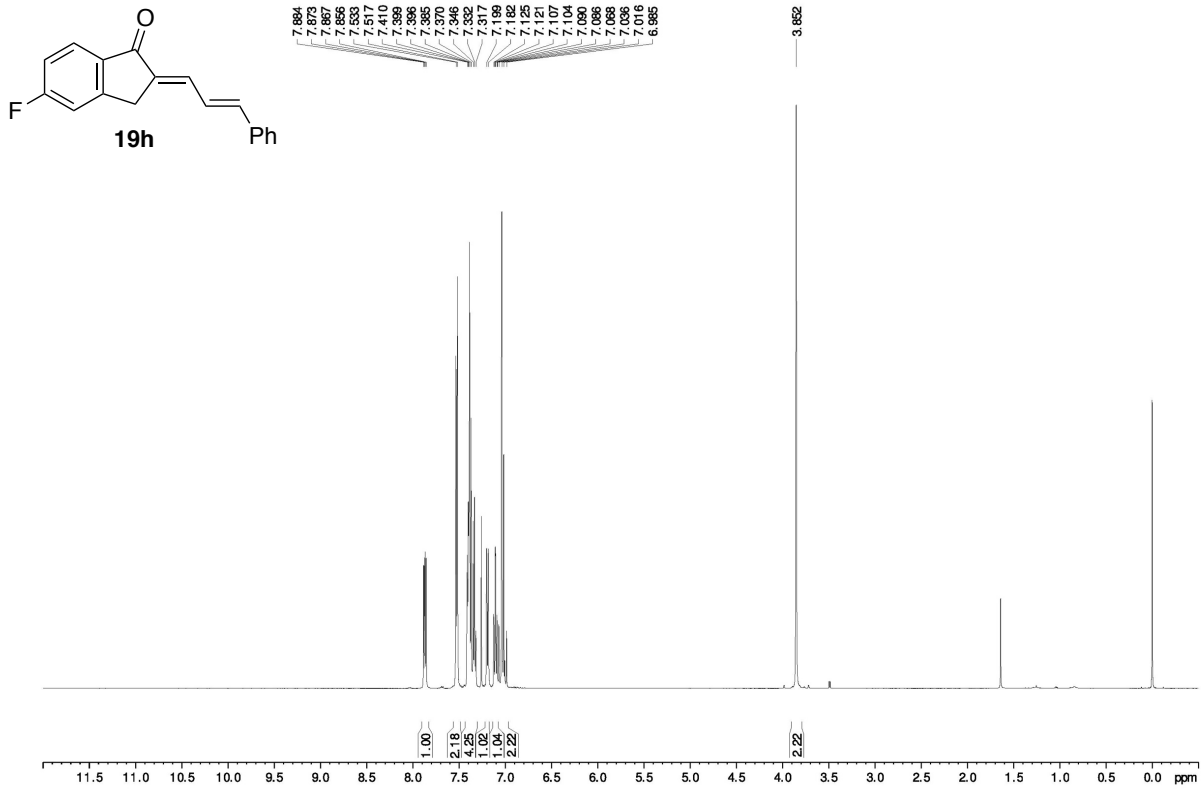
19g, ^{1}H NMR (500 MHz, $CDCl_3$)



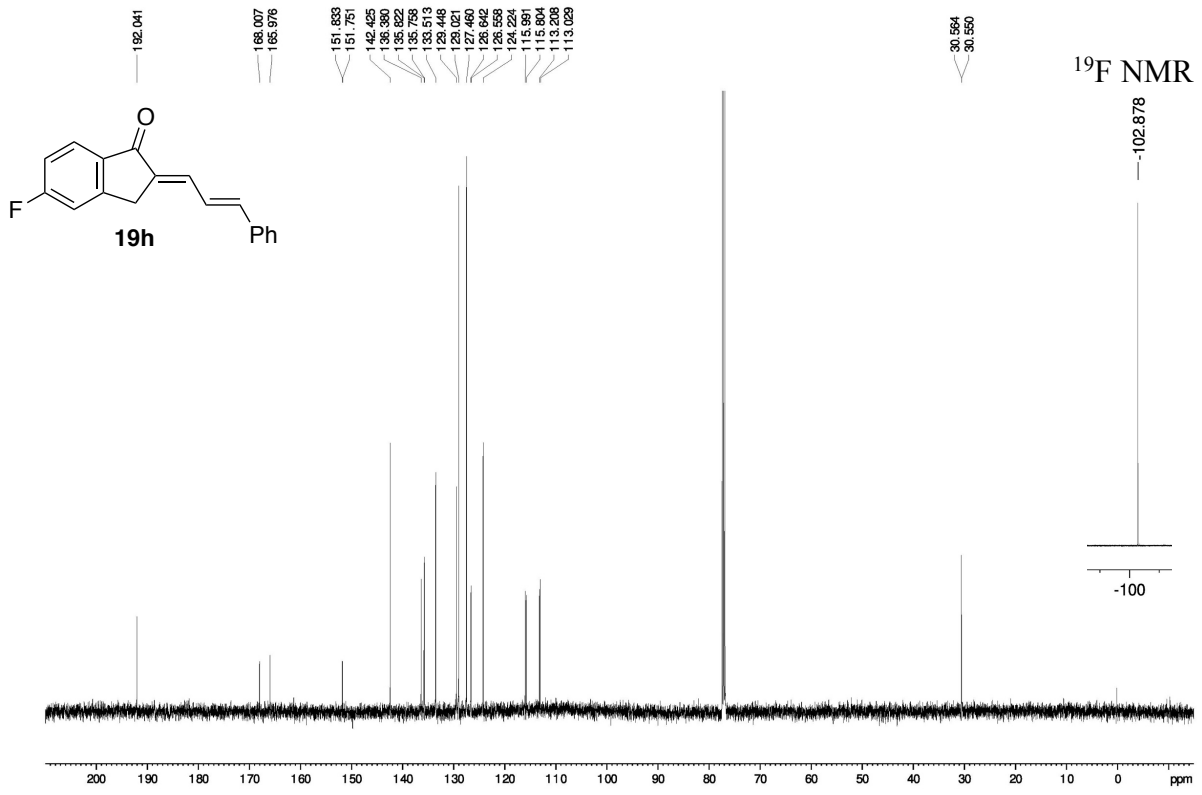
19g,^{13}C NMR (126 MHz, $CDCl_3$)



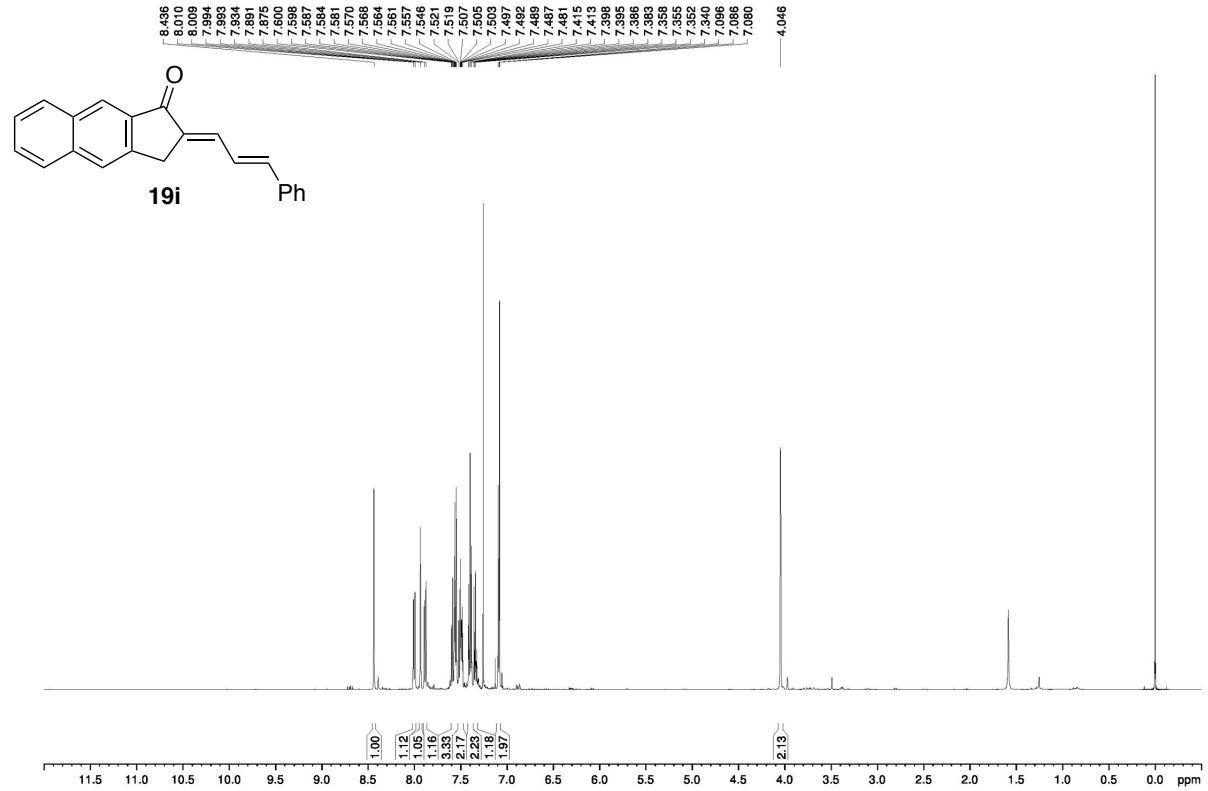
19h, ^{1}H NMR (500 MHz, $CDCl_3$)



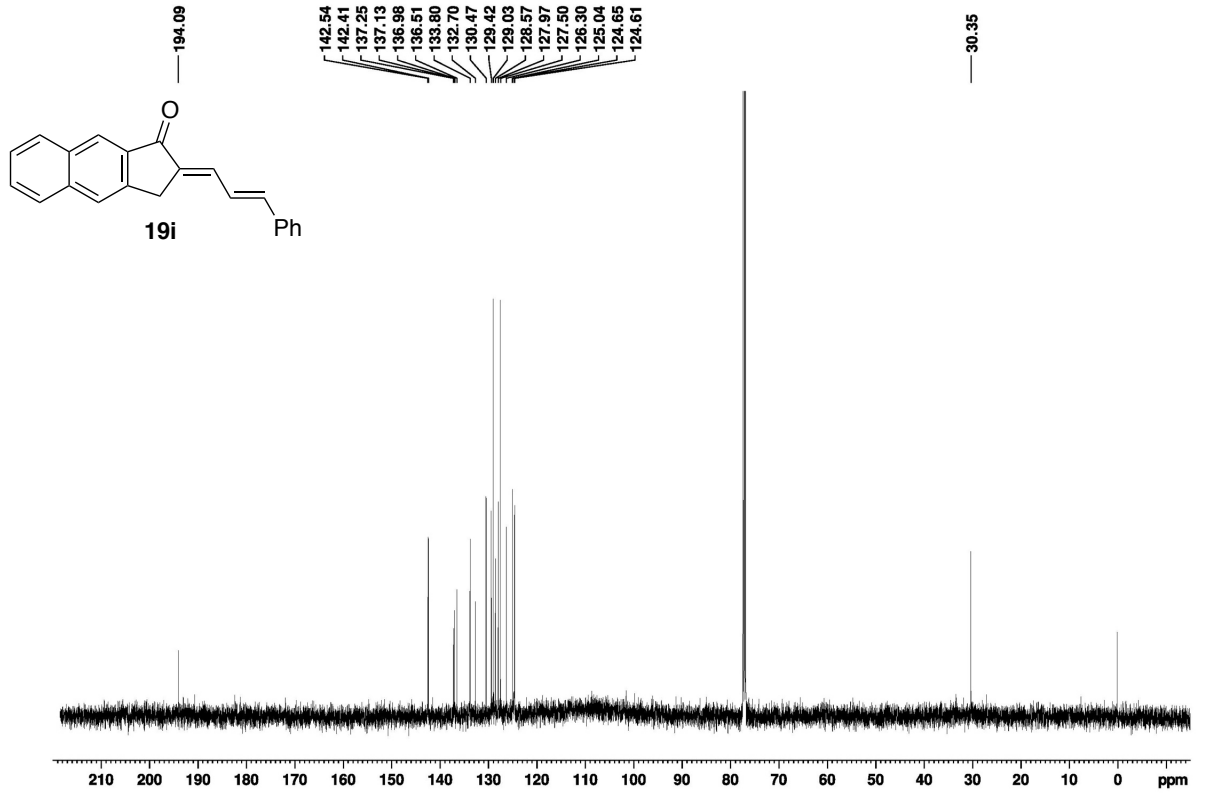
19h,^{13}C NMR (126 MHz, $CDCl_3$)



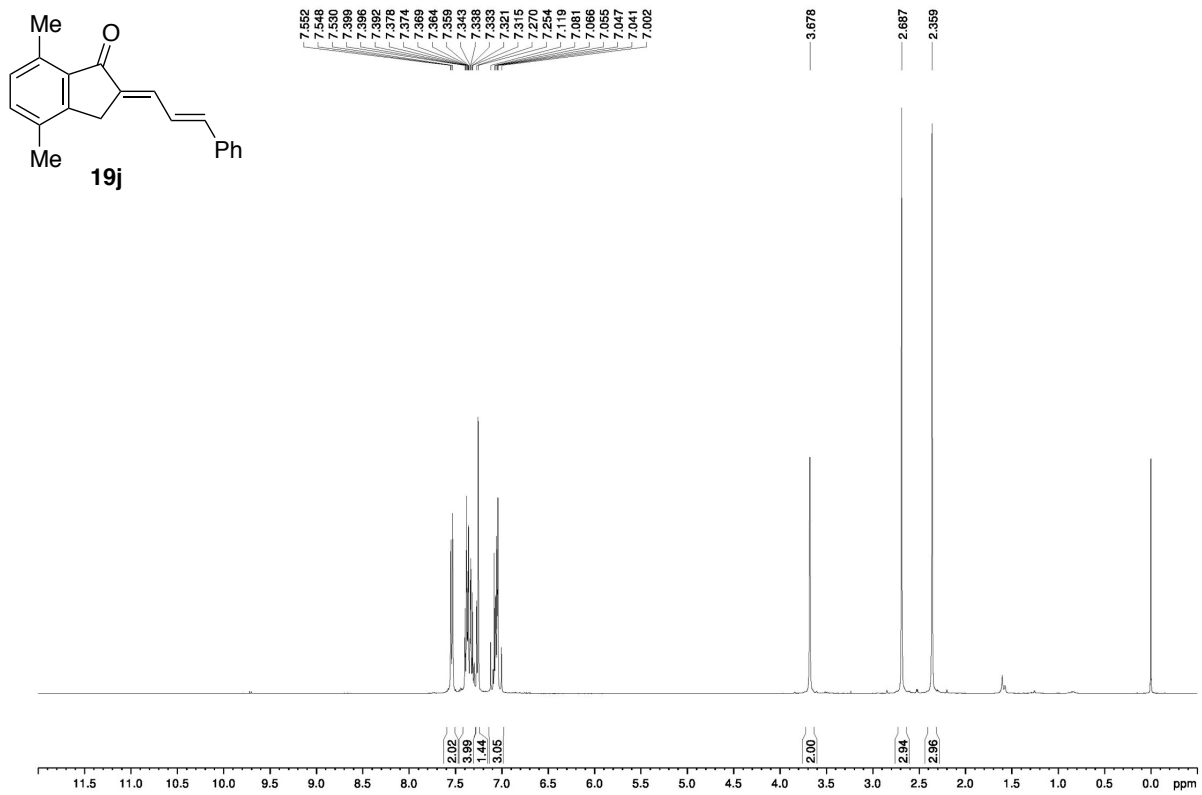
19i, ^{1}H NMR (500 MHz, $CDCl_3$)



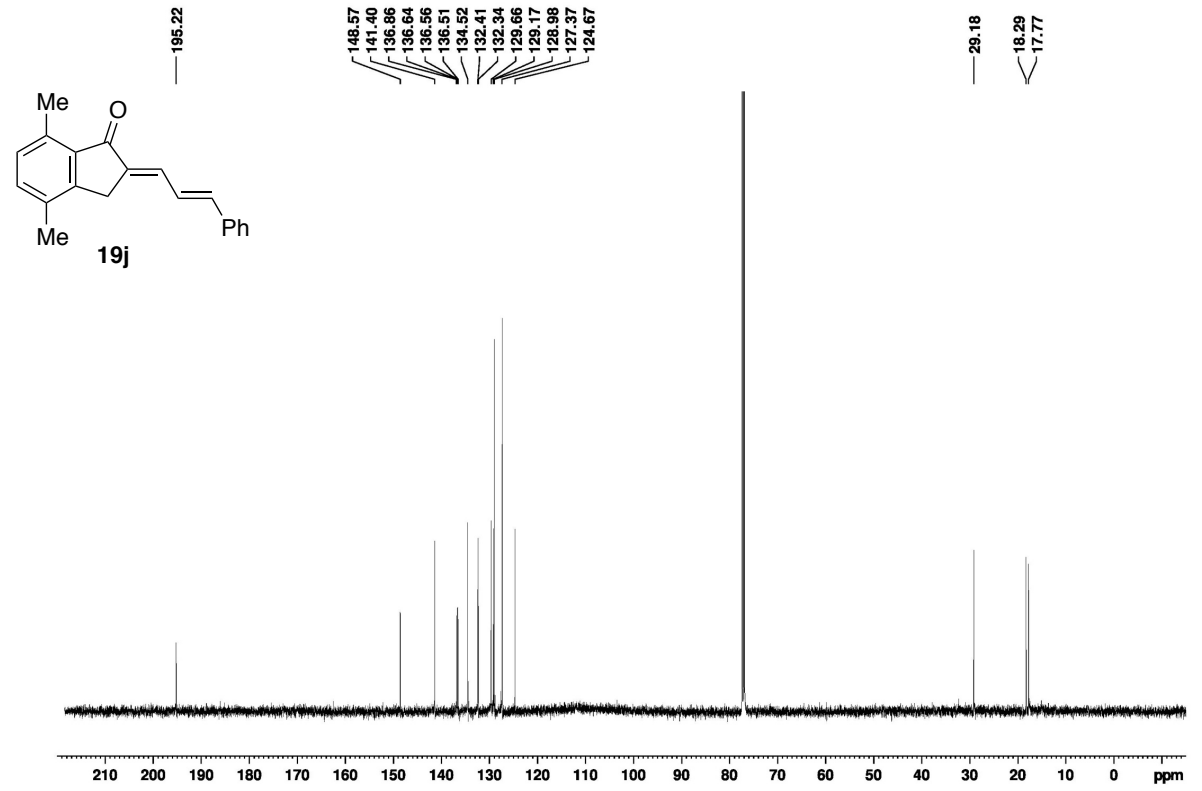
19i,^{13}C NMR (126 MHz, $CDCl_3$)



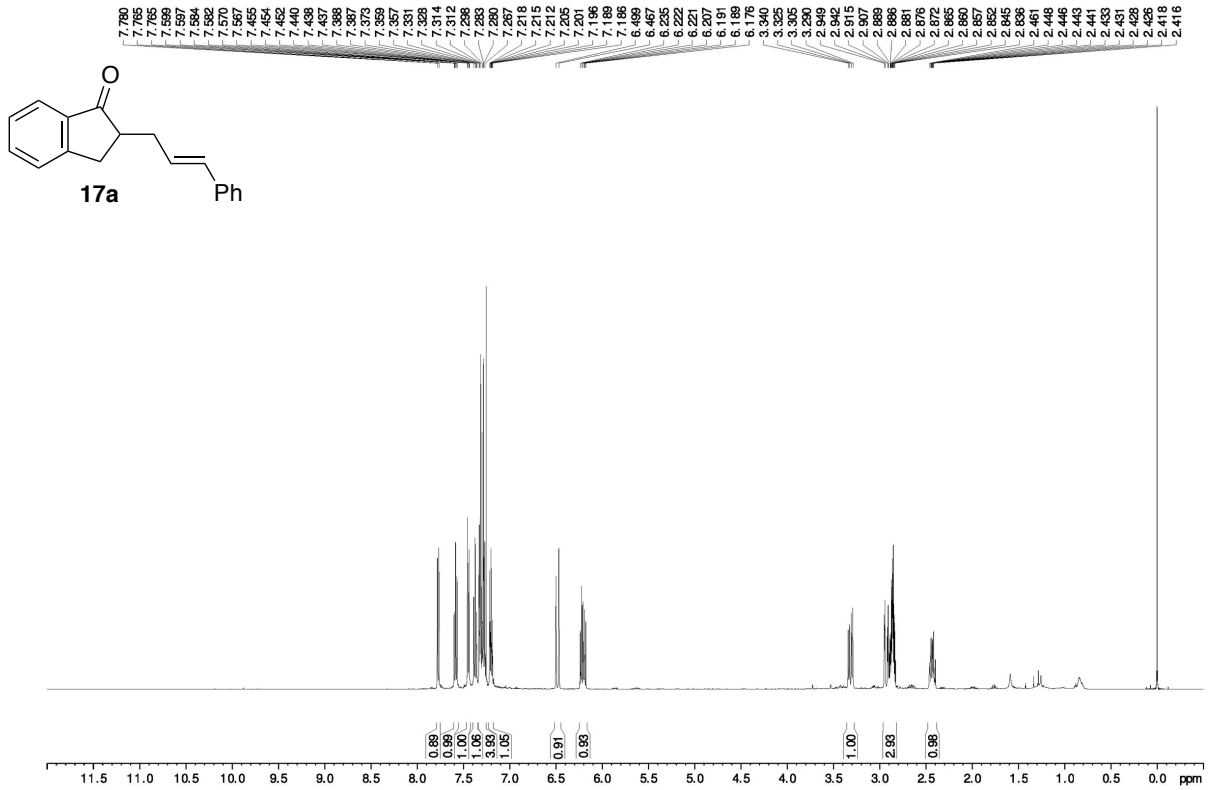
19j, ^{1}H NMR (400 MHz, $CDCl_3$)



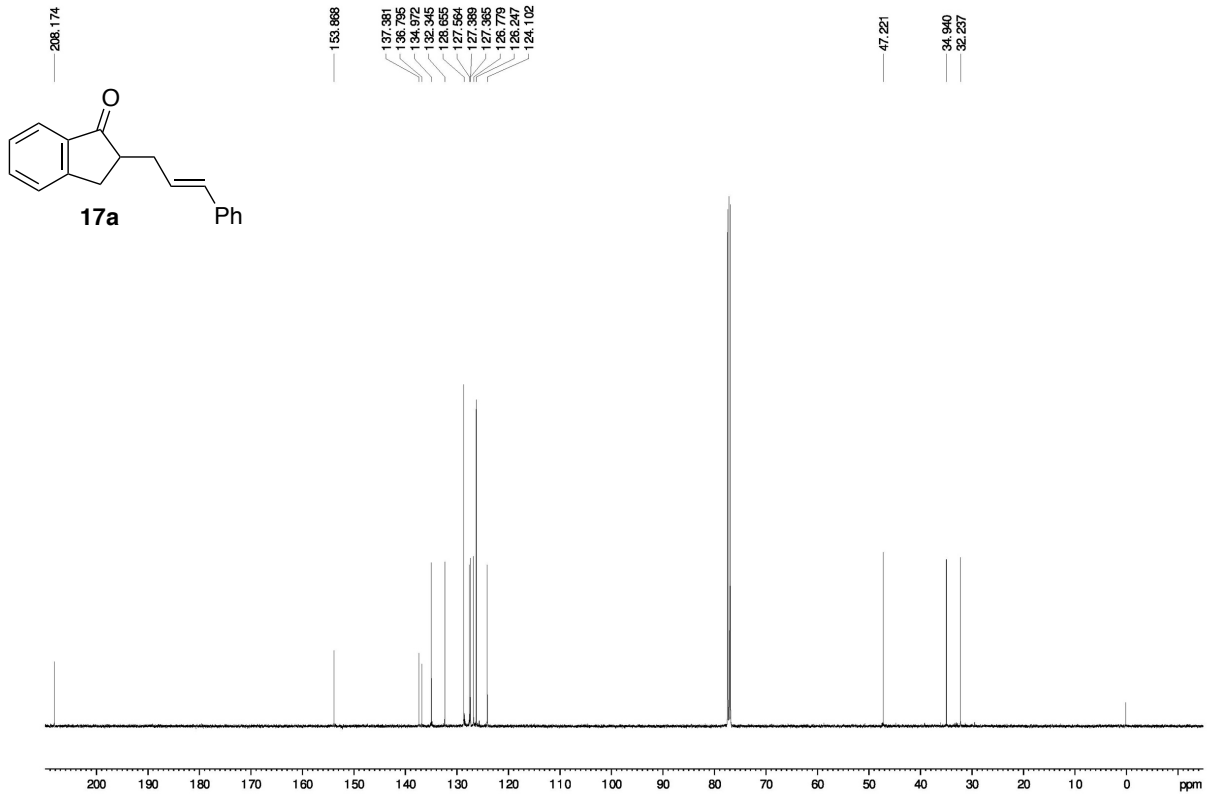
19j,^{13}C NMR (126 MHz, $CDCl_3$)



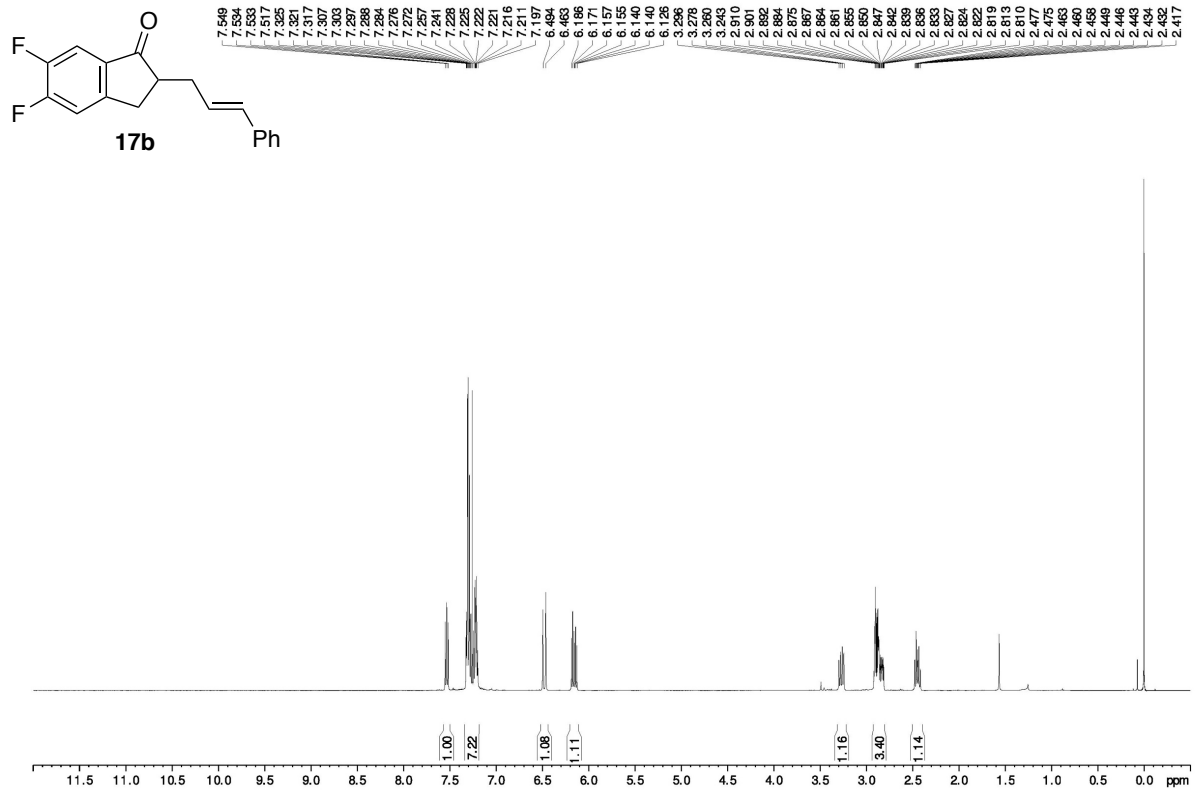
17a, ^{1}H NMR (500 MHz, $CDCl_3$)



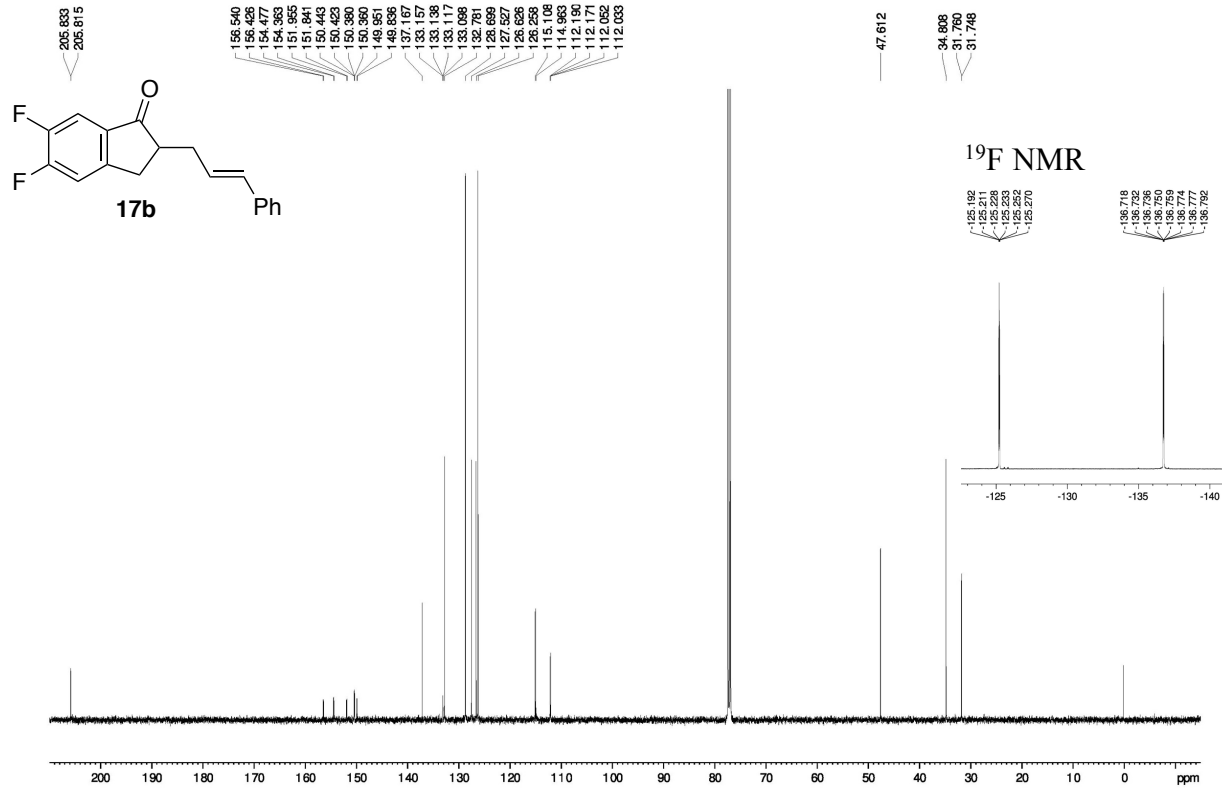
17a,^{13}C NMR (126 MHz, $CDCl_3$)



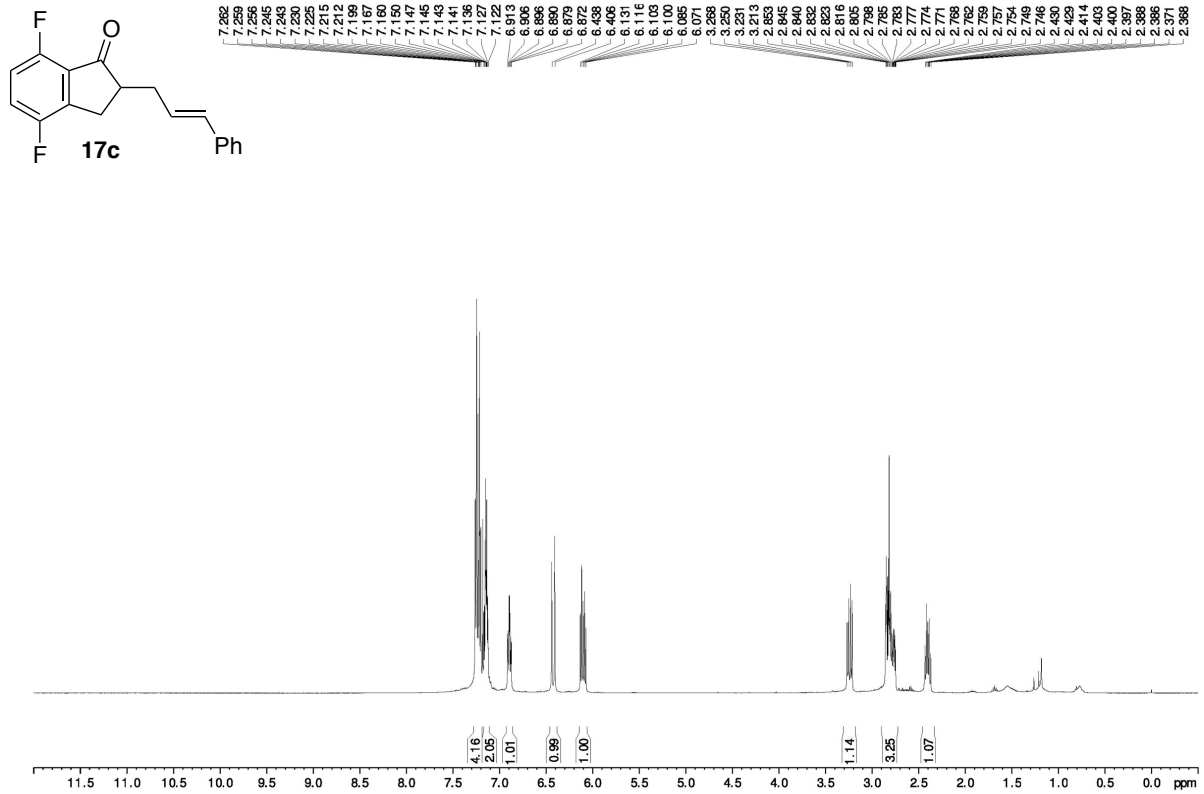
17b, ^{1}H NMR (500 MHz, $CDCl_3$)



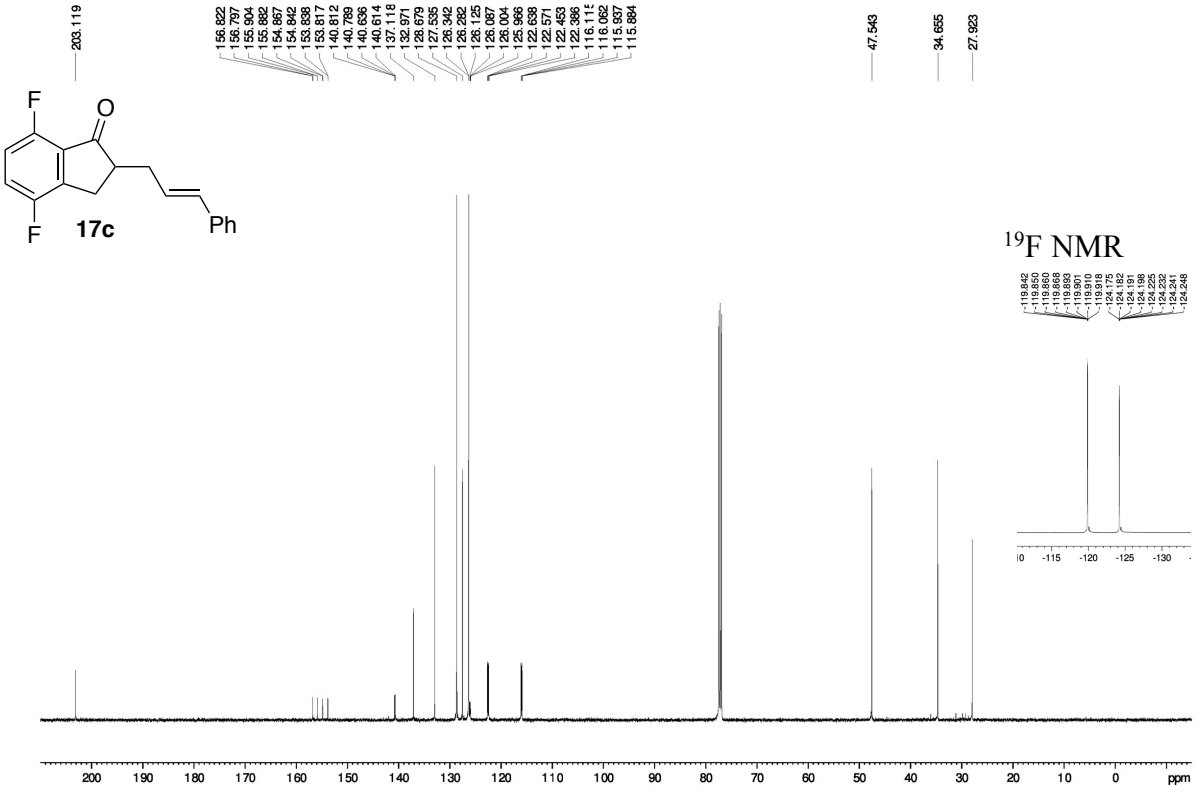
17b,^{13}C NMR (126 MHz, $CDCl_3$)



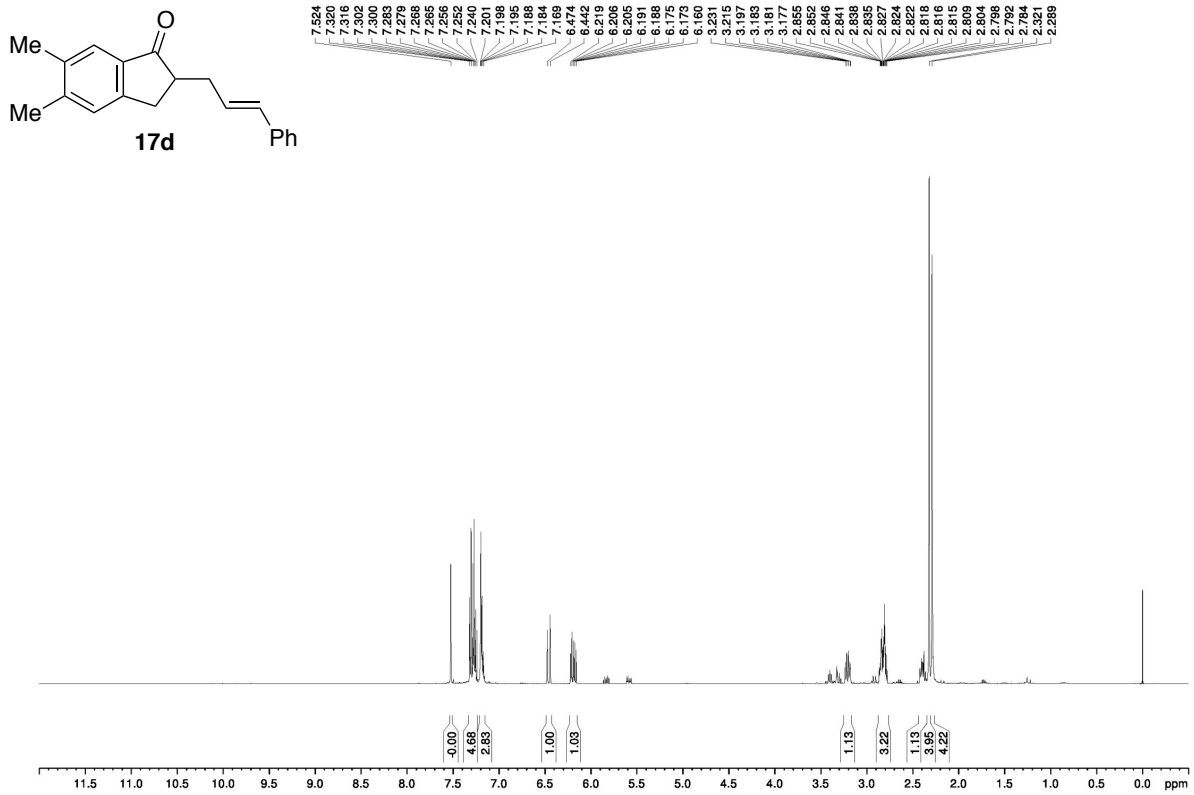
17c, ^{1}H NMR (500 MHz, $CDCl_3$)



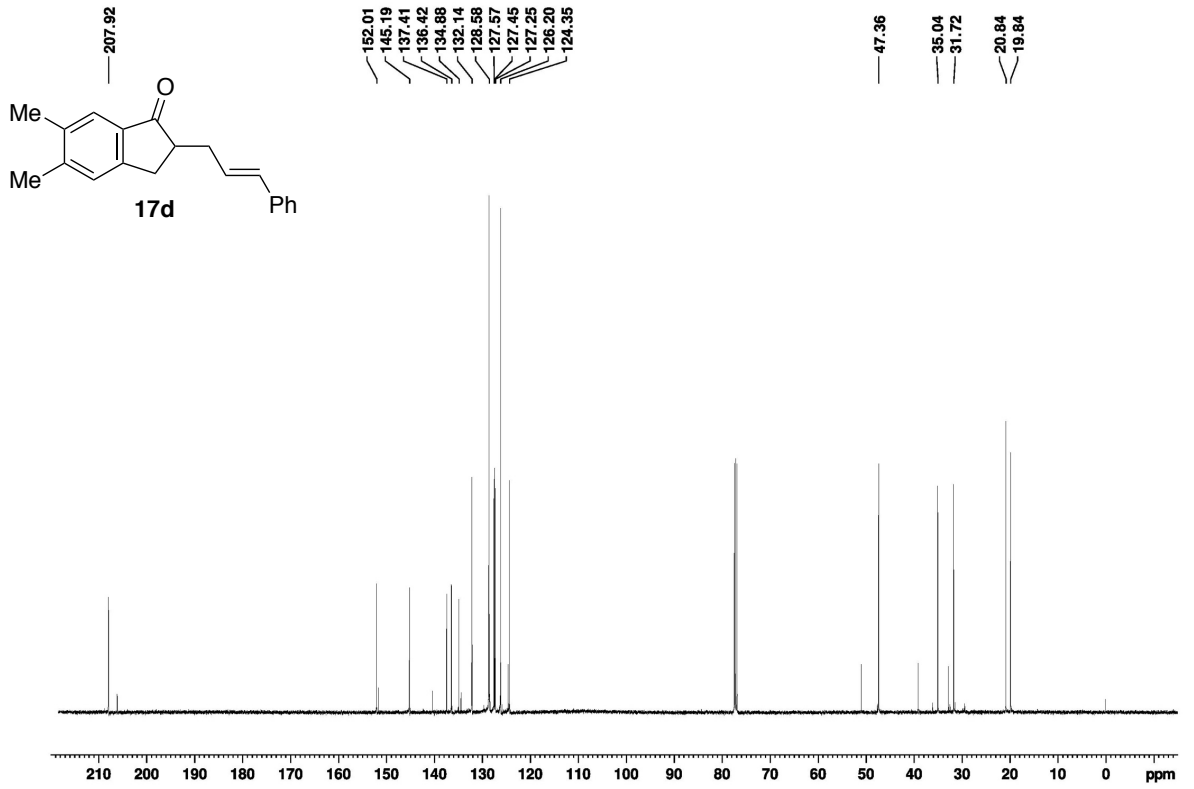
17c,^{13}C NMR (126 MHz, $CDCl_3$)



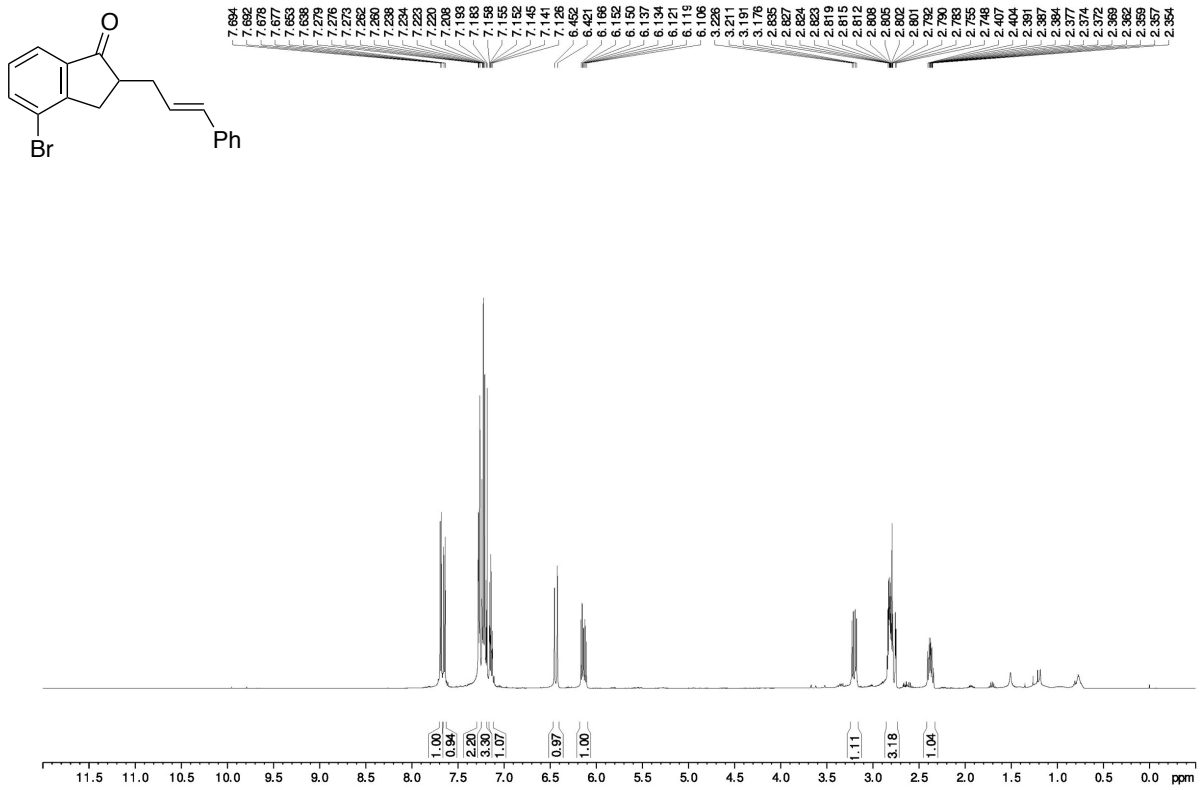
17d, ^{1}H NMR (500 MHz, $CDCl_3$)



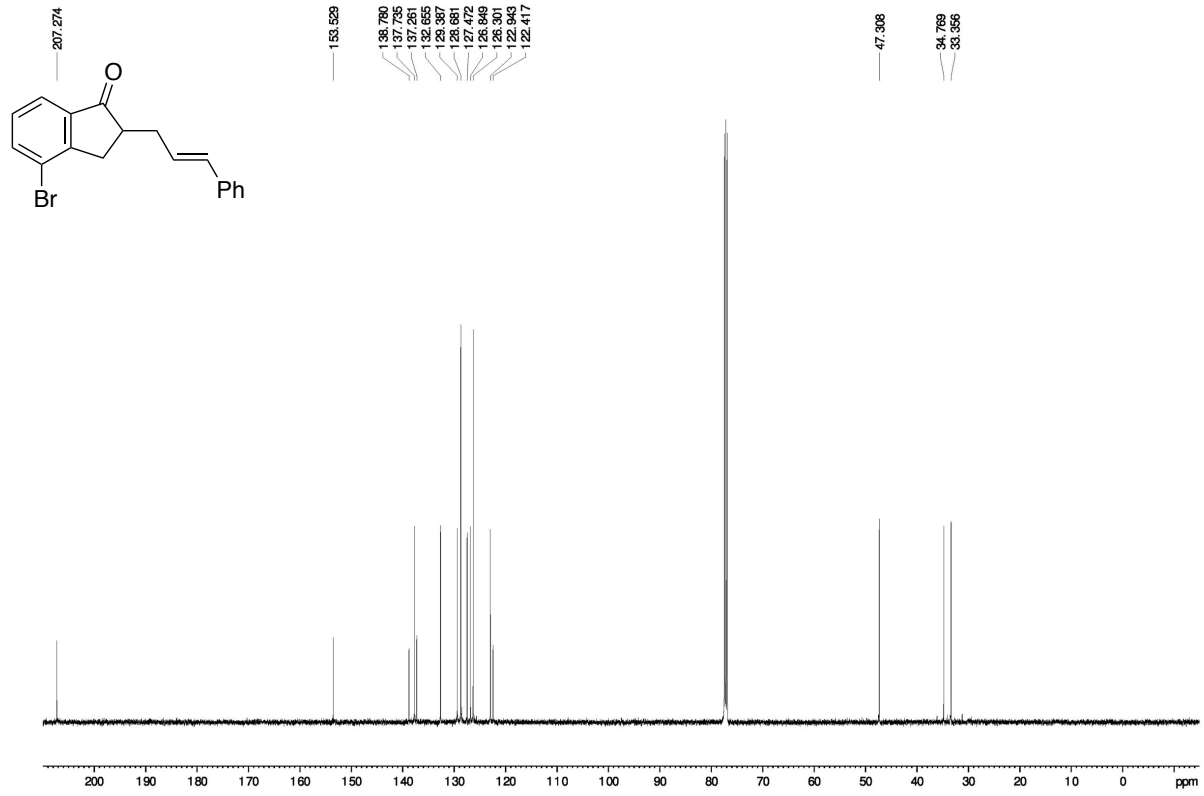
17d,^{13}C NMR (126 MHz, $CDCl_3$)



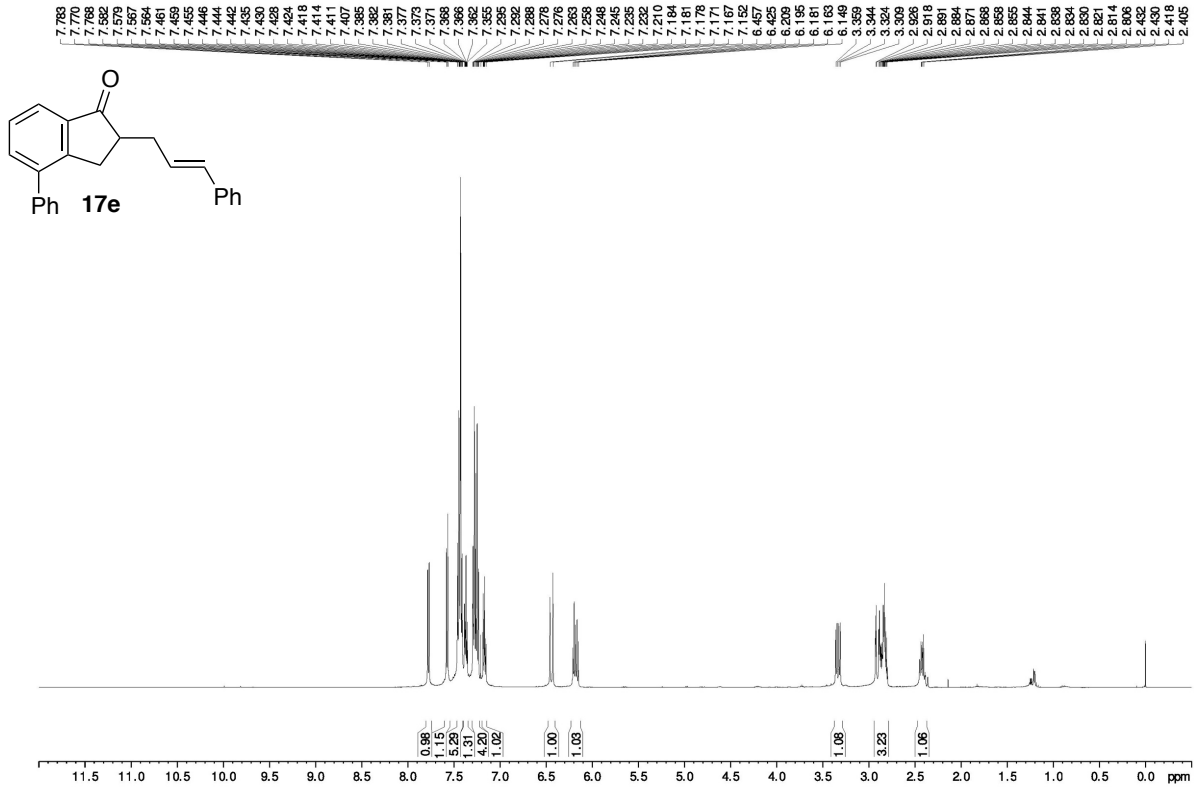
4-Bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one, ^{1}H NMR (500 MHz, $CDCl_3$)



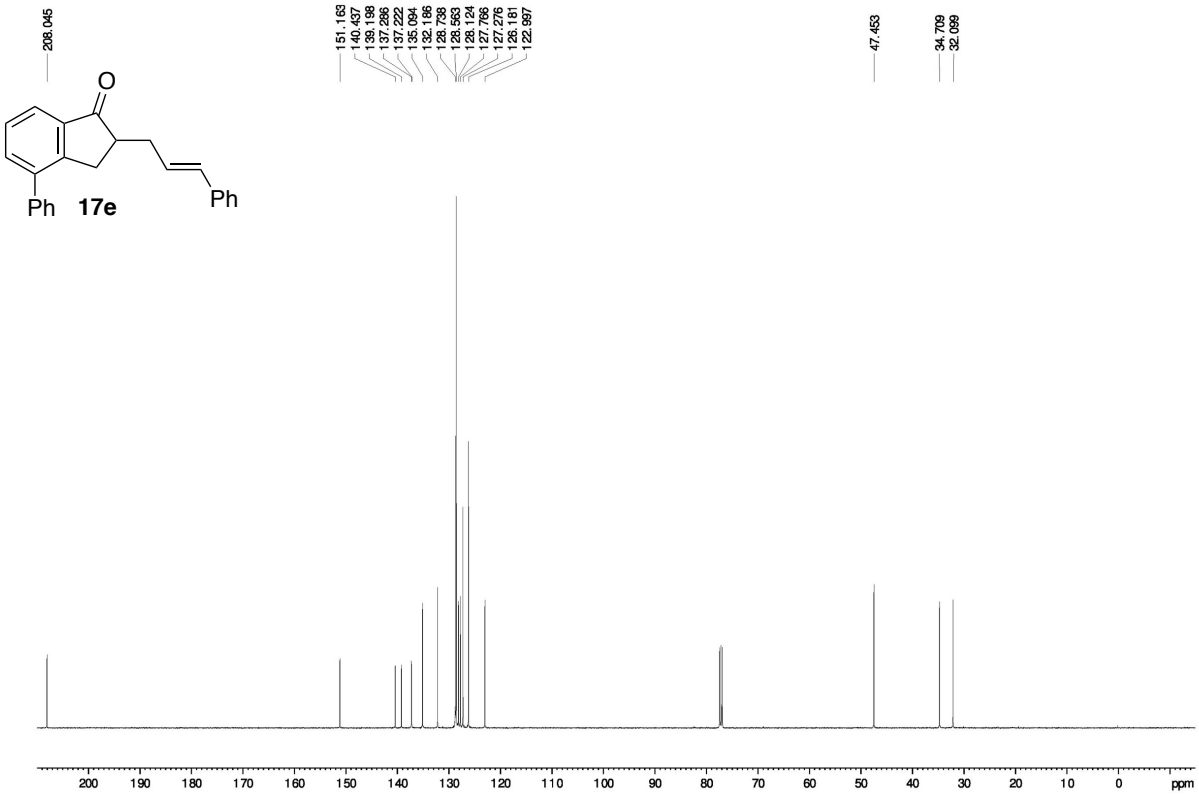
4-Bromo-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one, ^{13}C NMR (126 MHz, $CDCl_3$)



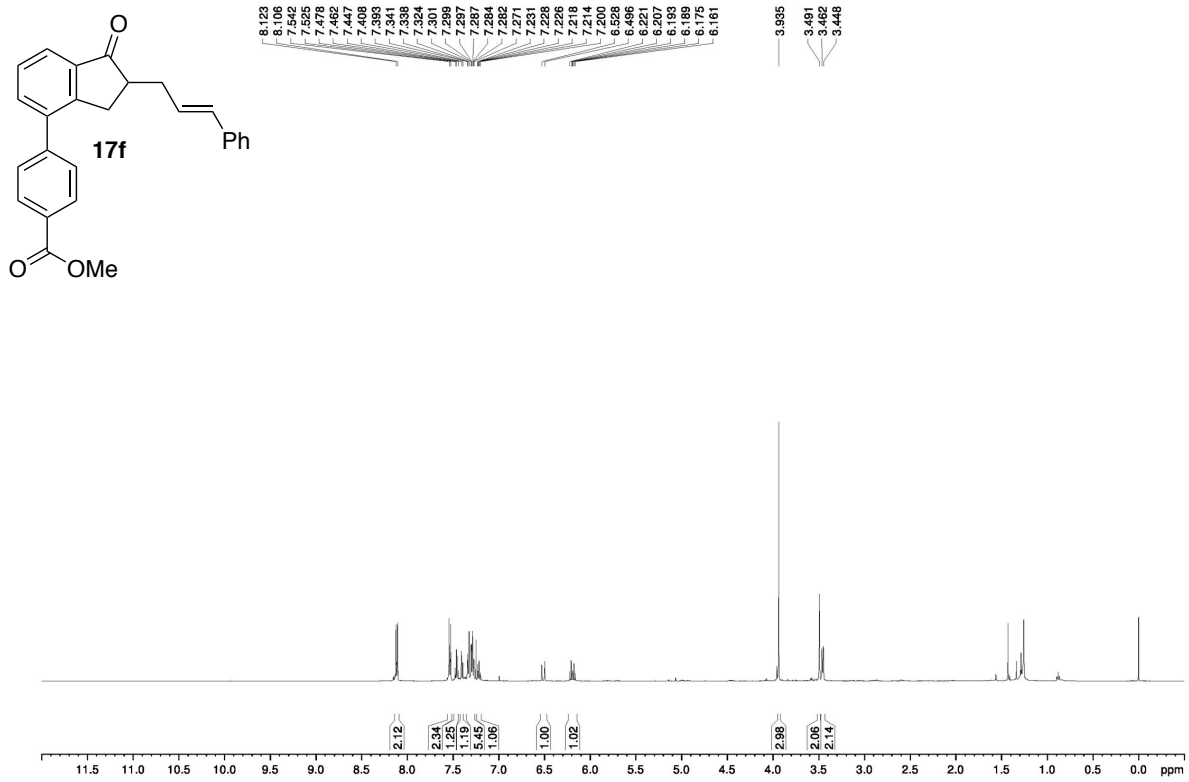
17e, ^{1}H NMR (500 MHz, $CDCl_3$)



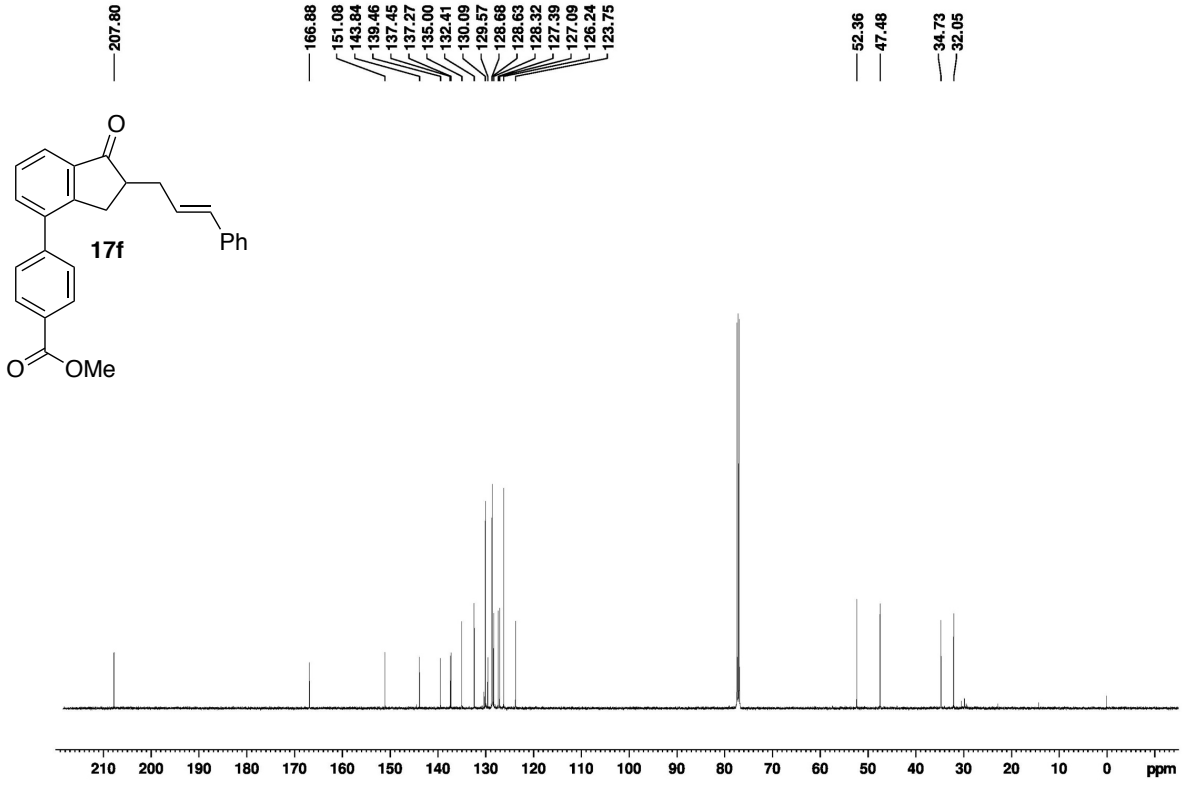
17e,^{13}C NMR (126 MHz, $CDCl_3$)



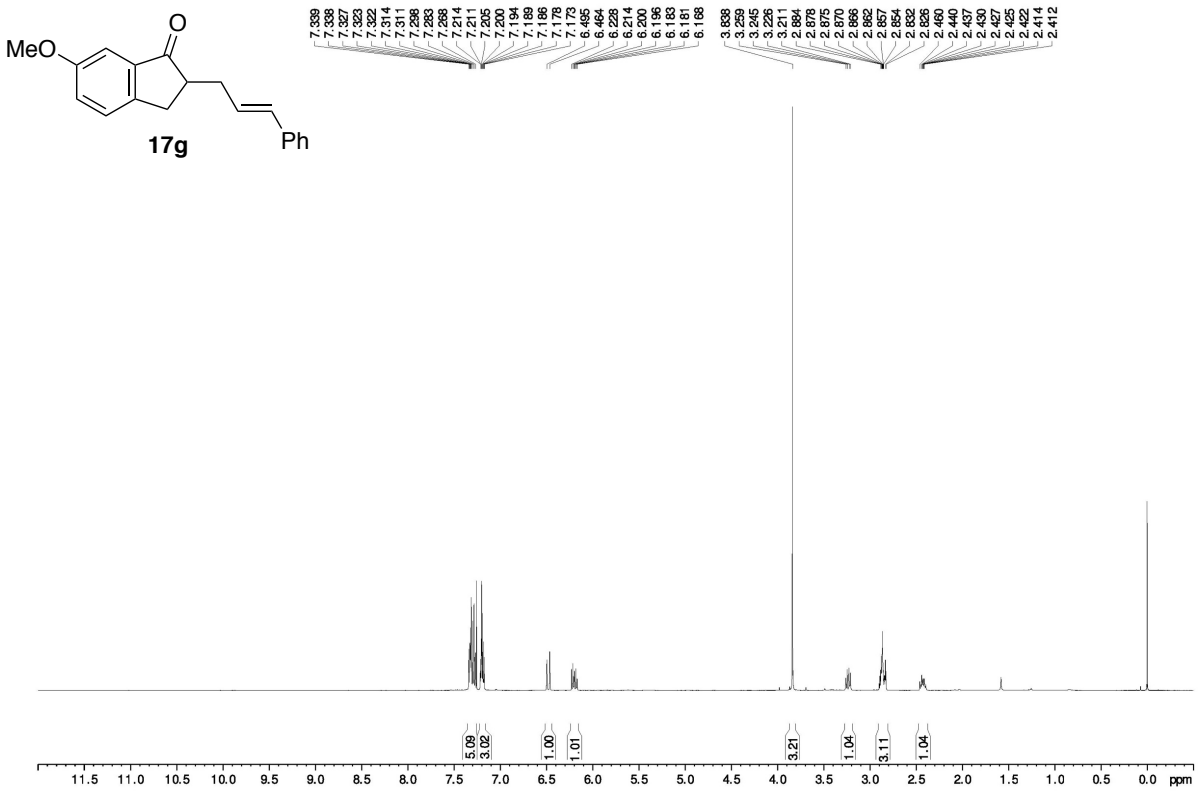
17f, ^{1}H NMR (500 MHz, $CDCl_3$)



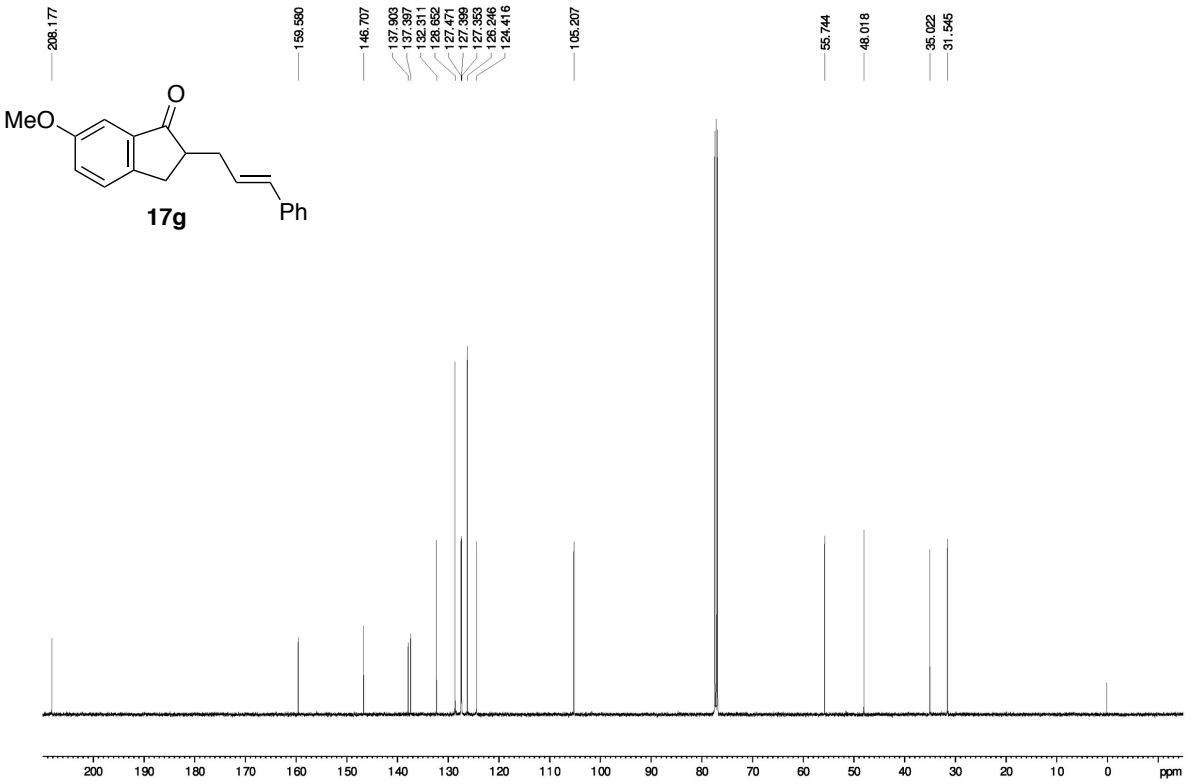
17f,^{13}C NMR (126 MHz, $CDCl_3$)



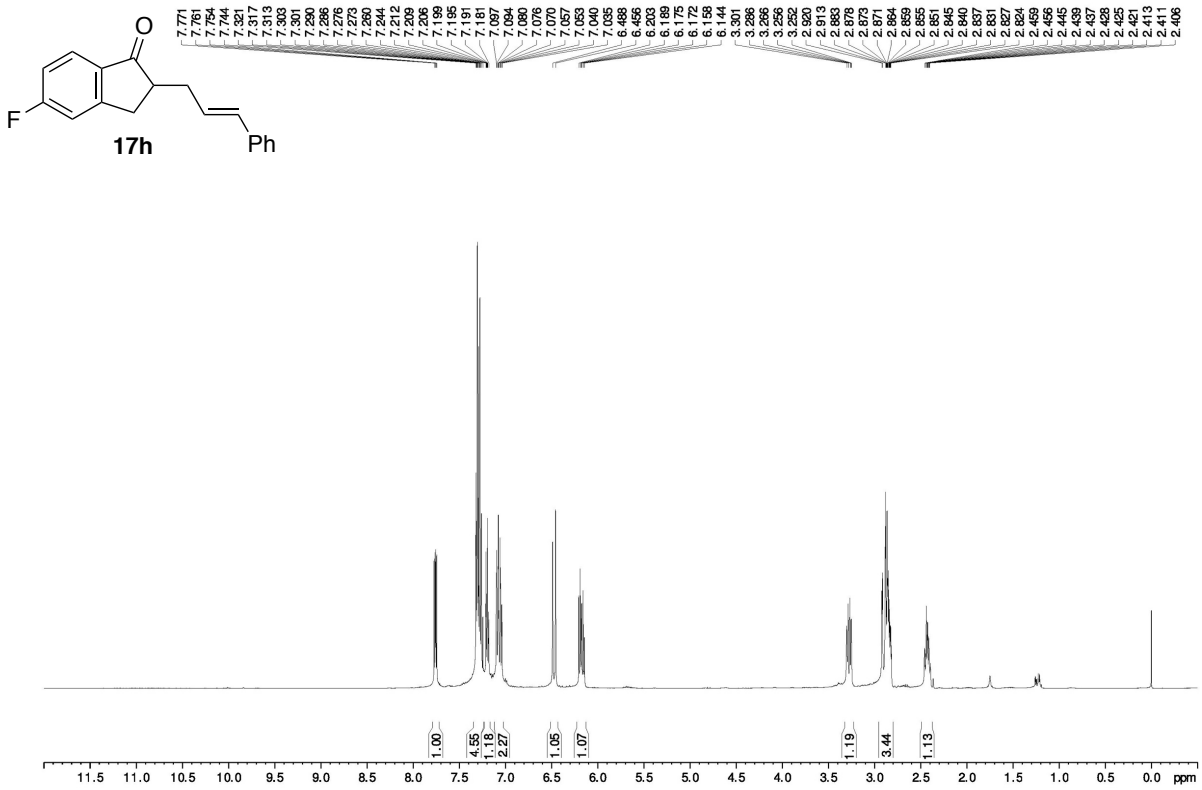
17g, ^{1}H NMR (500 MHz, $CDCl_3$)



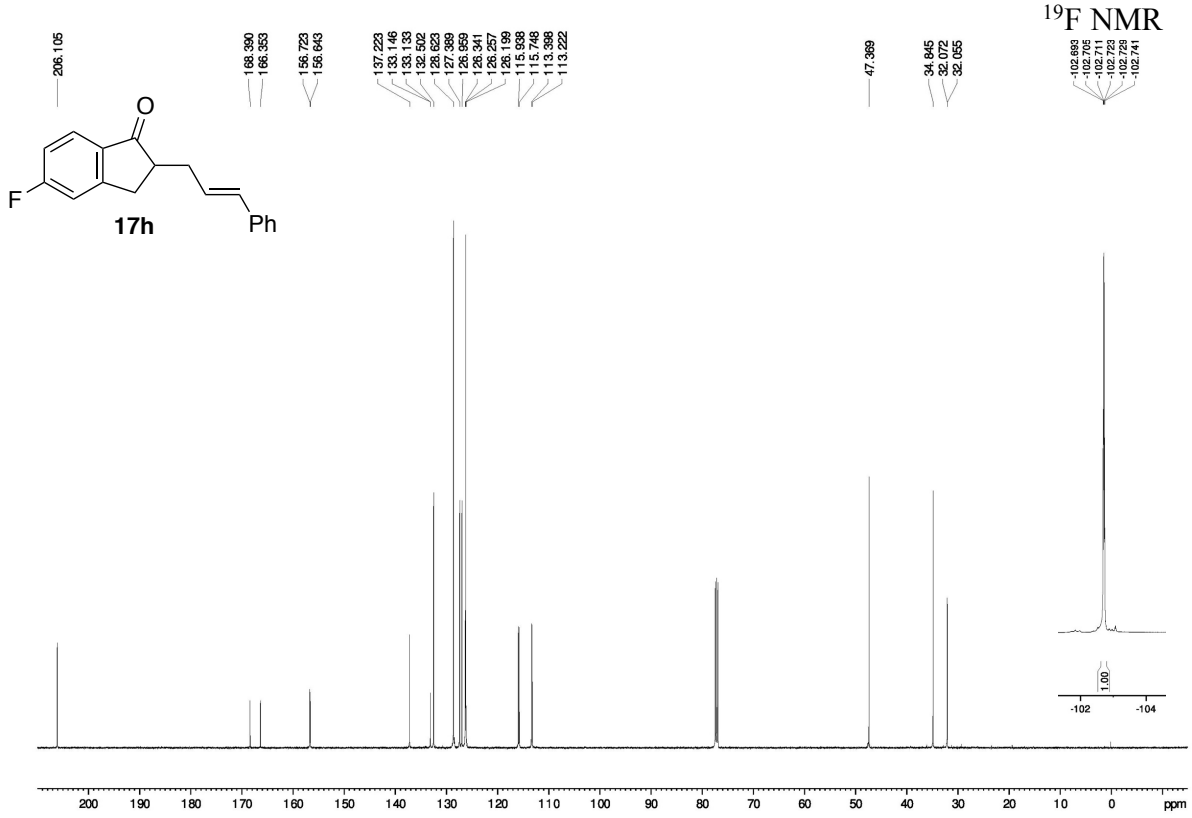
17g,^{13}C NMR (126 MHz, $CDCl_3$)



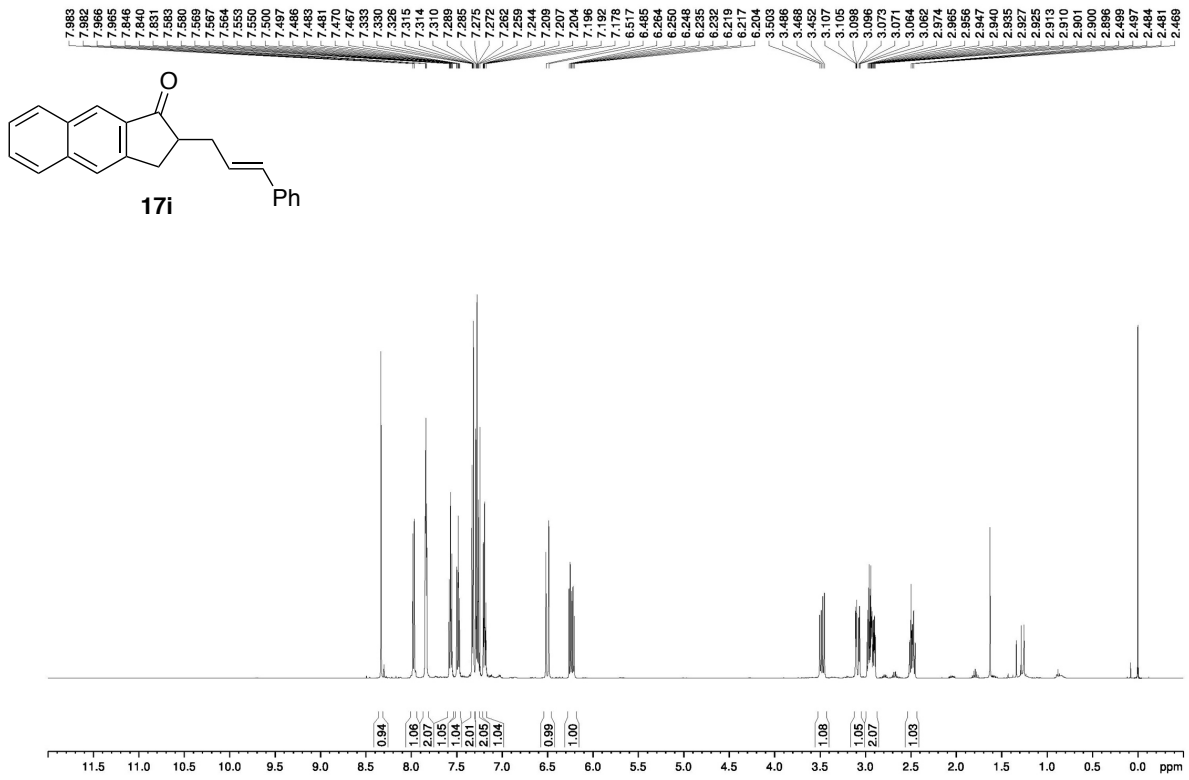
17h, ^{1}H NMR (500 MHz, $CDCl_3$)



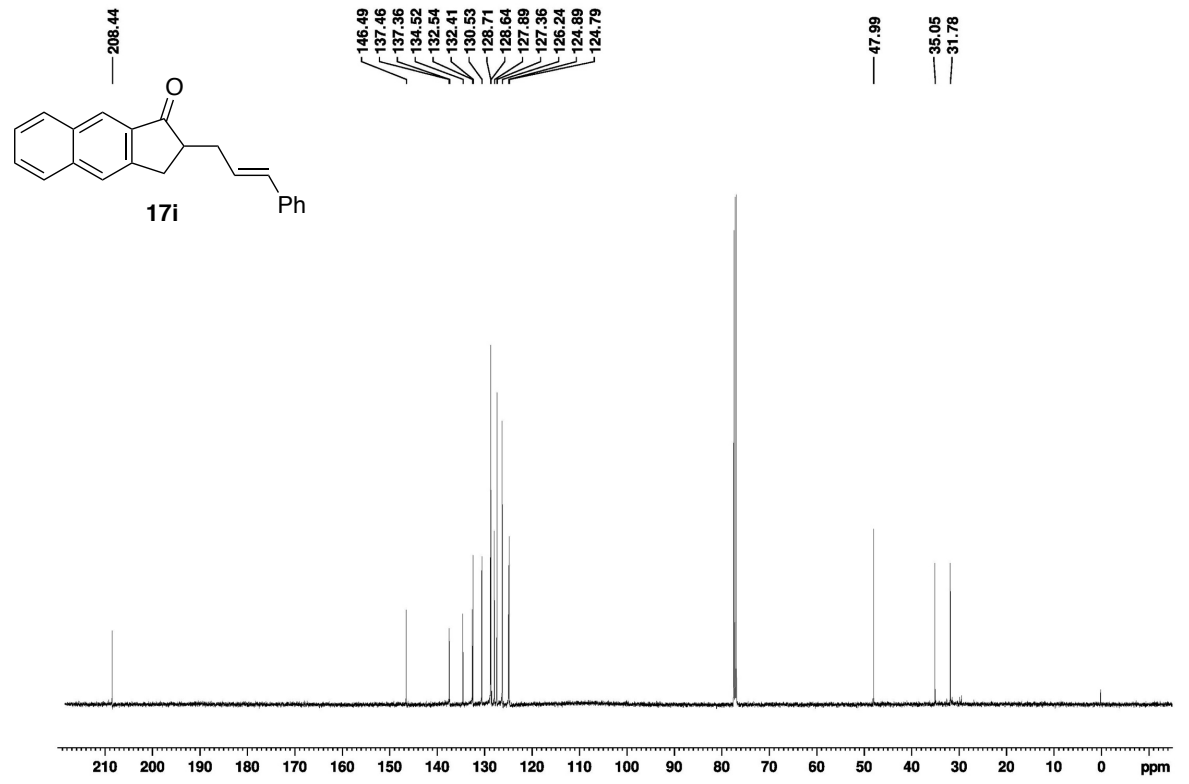
17h,^{13}C NMR (126 MHz, $CDCl_3$)



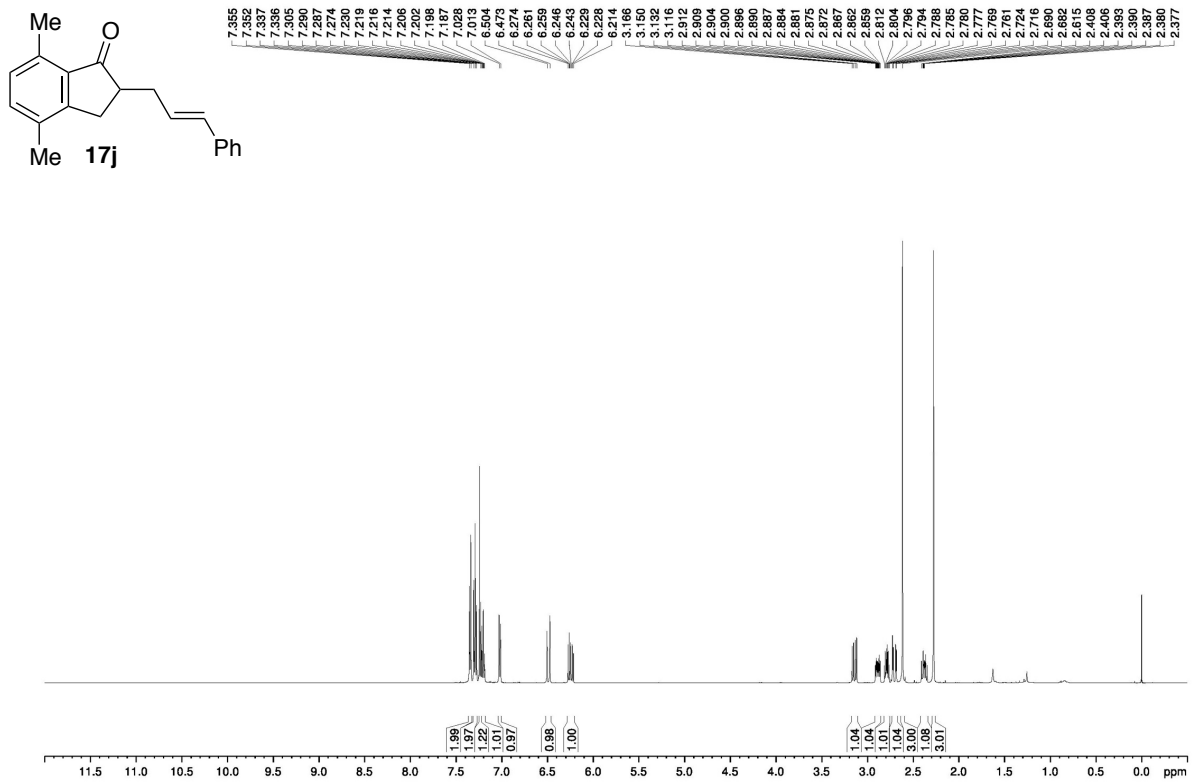
17i, ^{1}H NMR (500 MHz, $CDCl_3$)



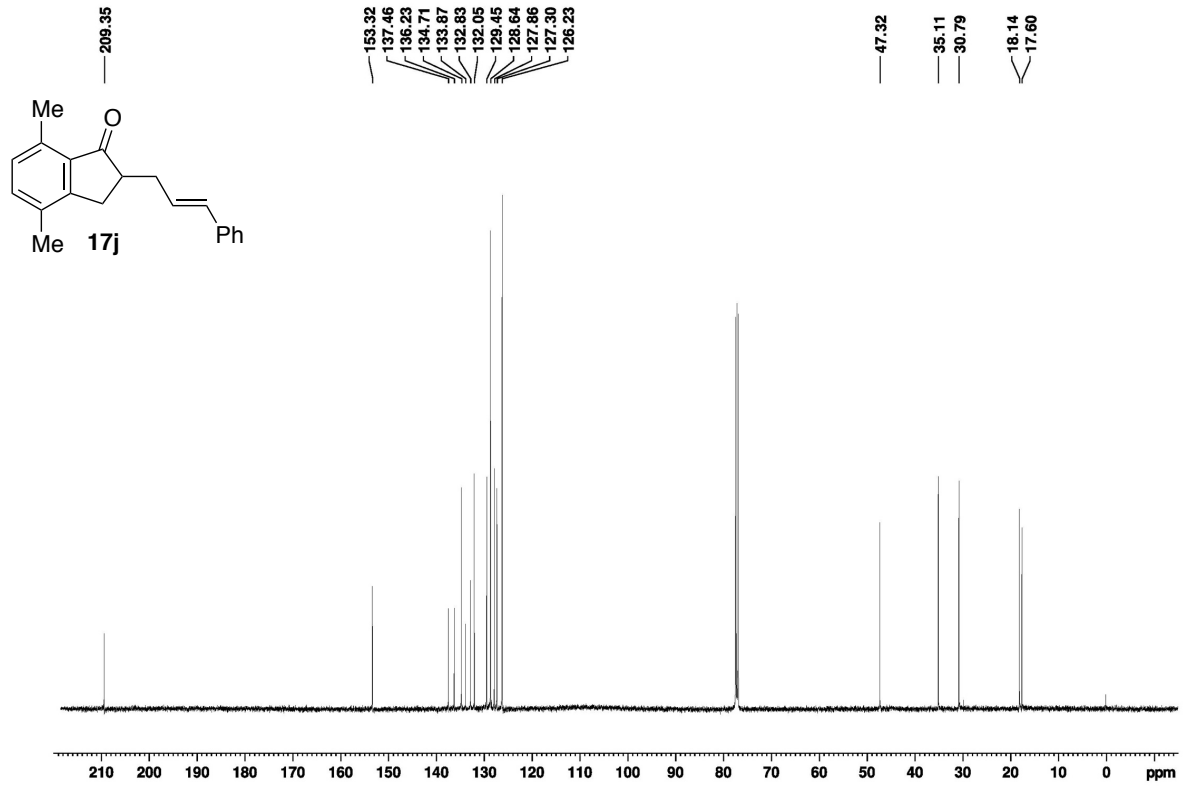
17i,^{13}C NMR (126 MHz, $CDCl_3$)



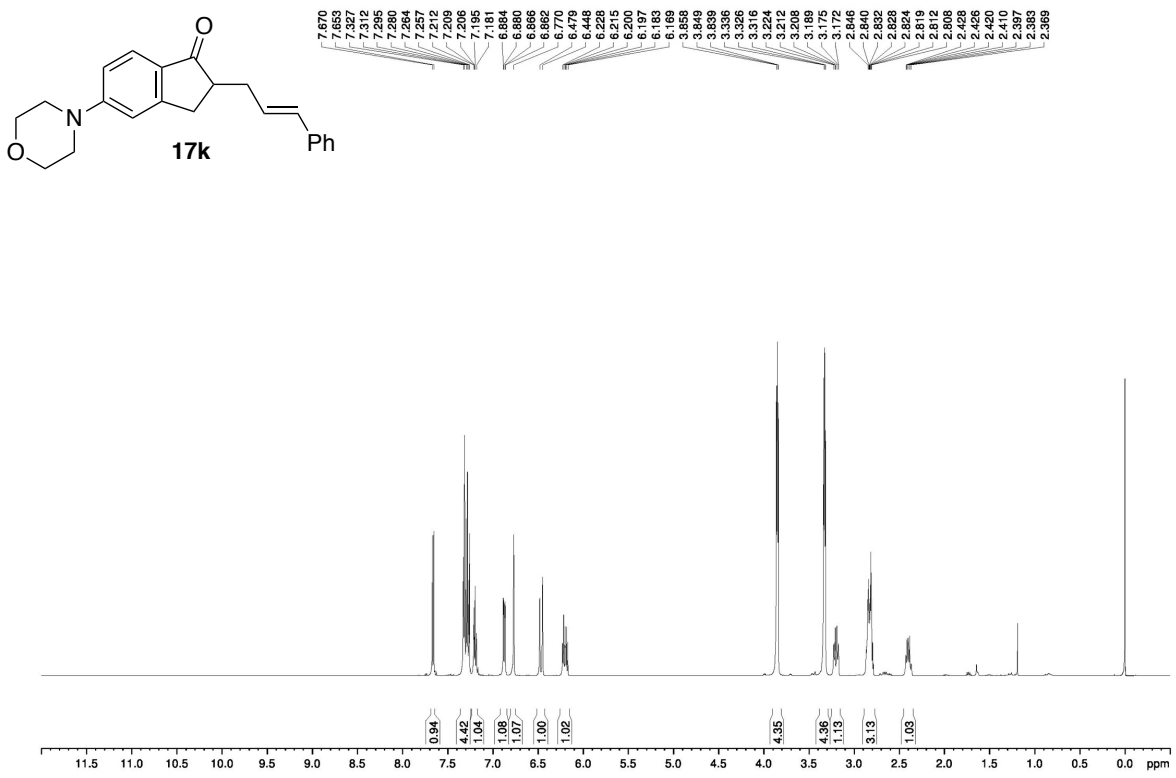
17j, ^{1}H NMR (500 MHz, $CDCl_3$)



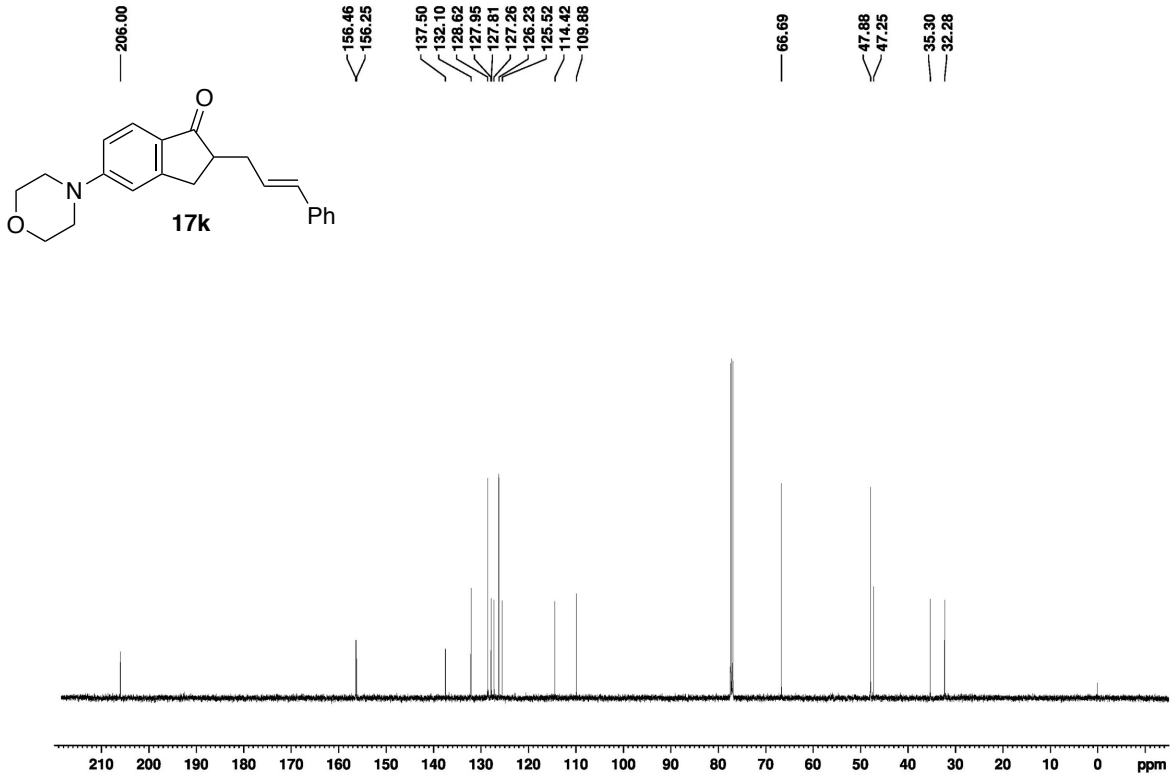
17j,^{13}C NMR (126 MHz, $CDCl_3$)



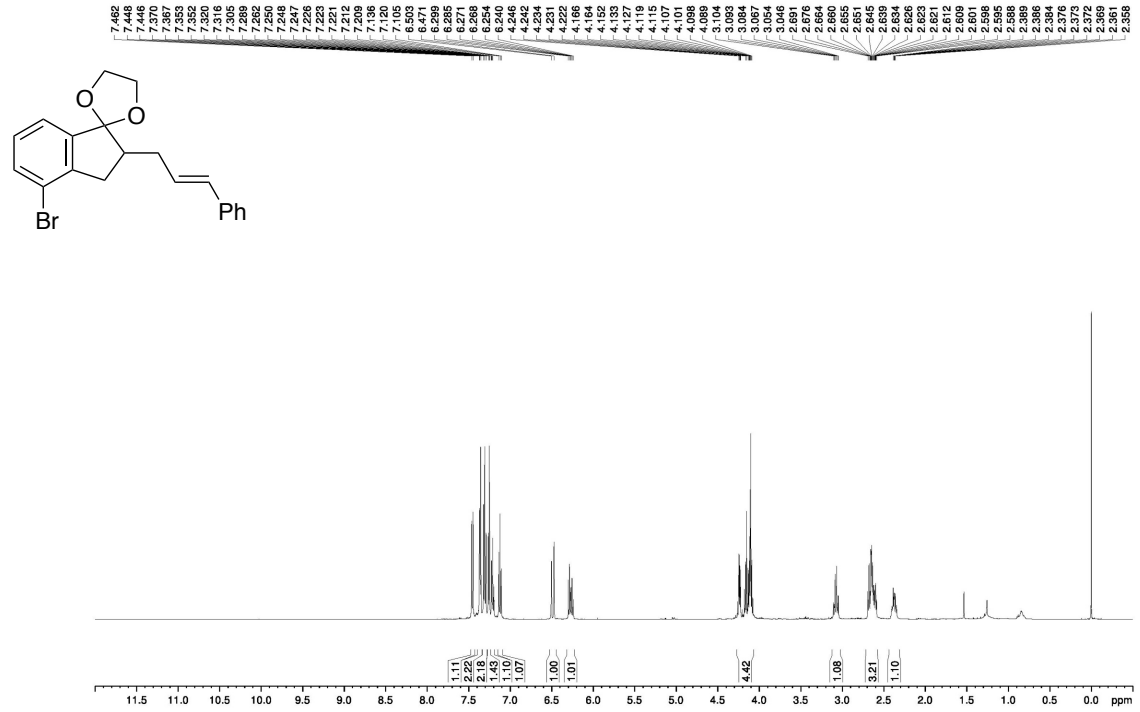
17k, ^{1}H NMR (500 MHz, $CDCl_3$)



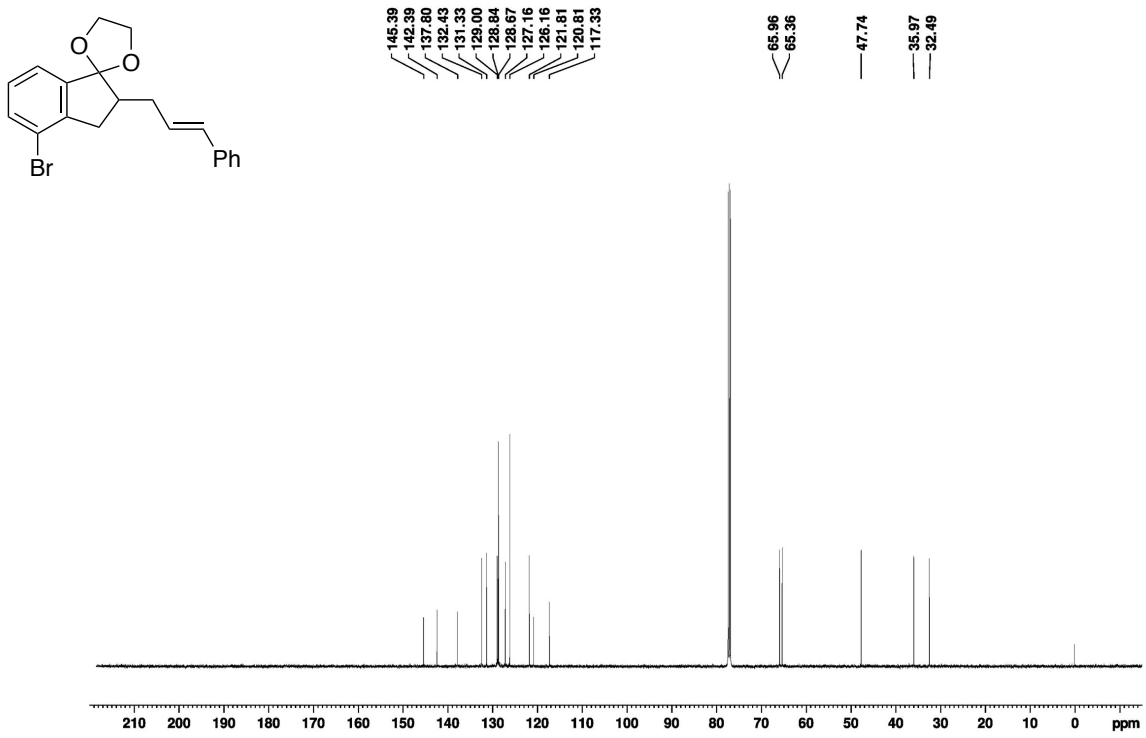
17k,^{13}C NMR (126 MHz, $CDCl_3$)



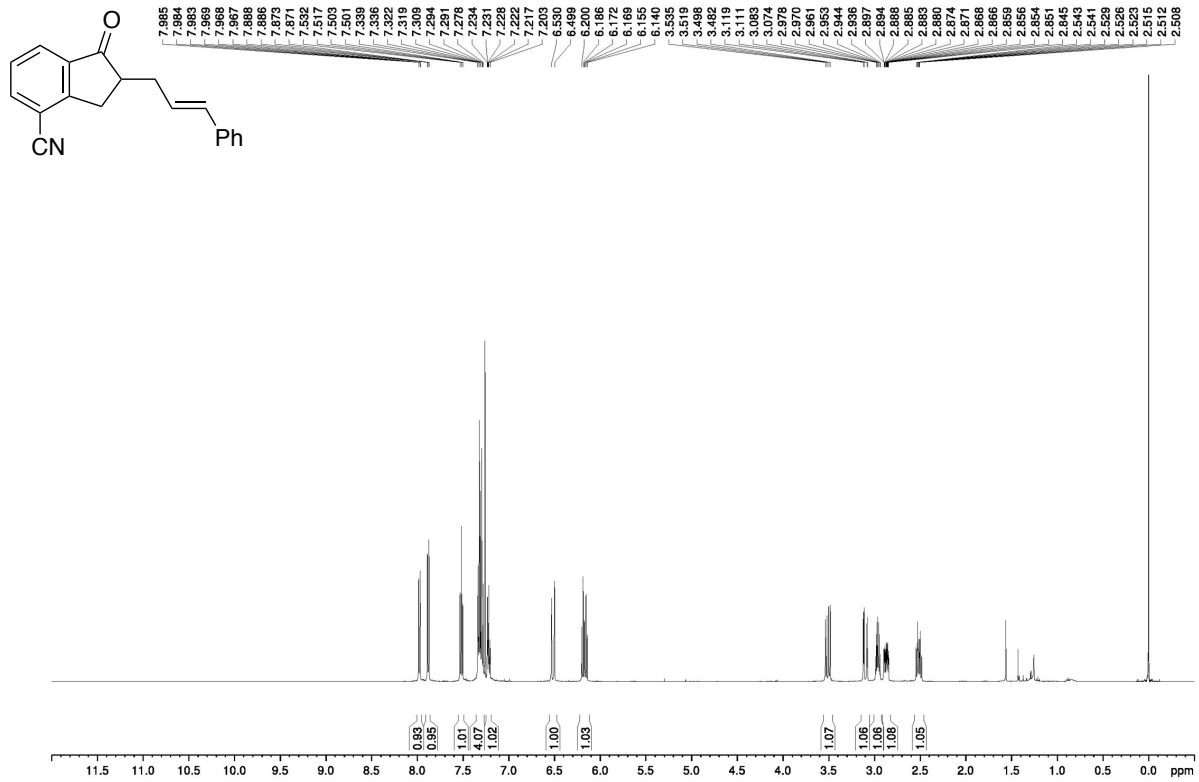
4-Bromo-2-cinnamyl-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane], ^{1}H NMR (500 MHz, $CDCl_3$)



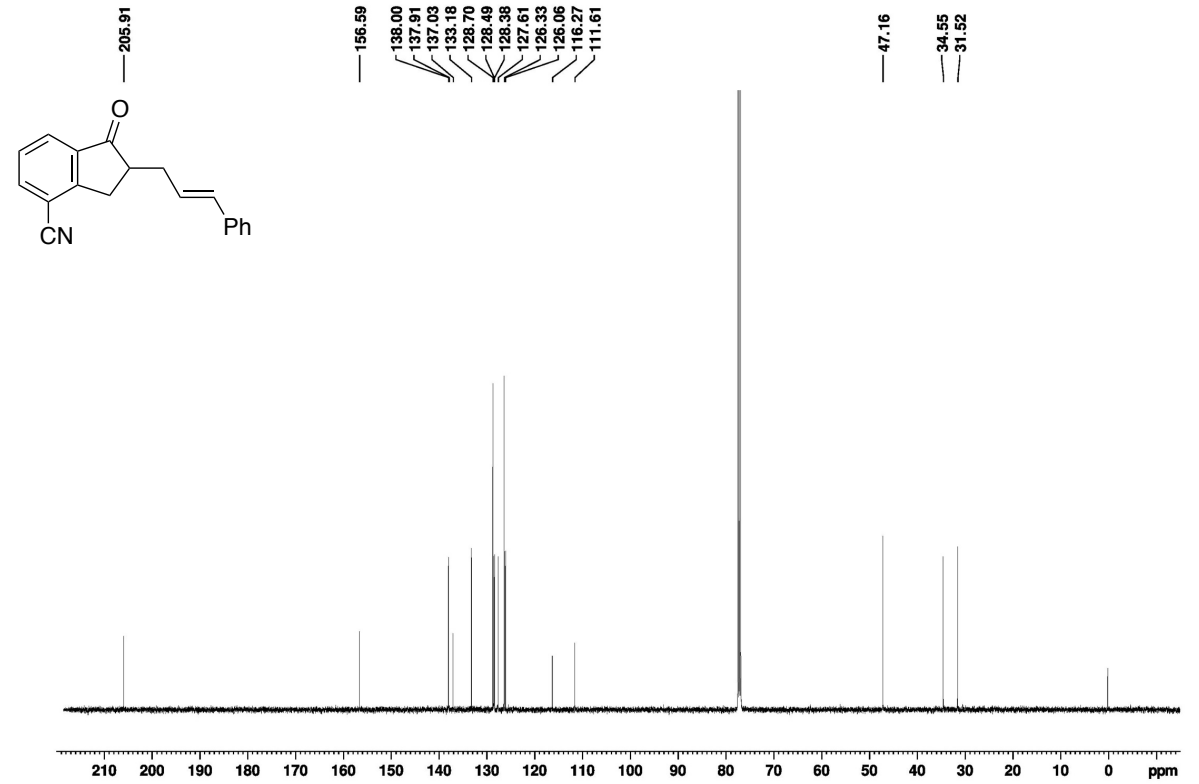
4-Bromo-2-cinnamyl-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane], ^{13}C NMR (126 MHz, $CDCl_3$)



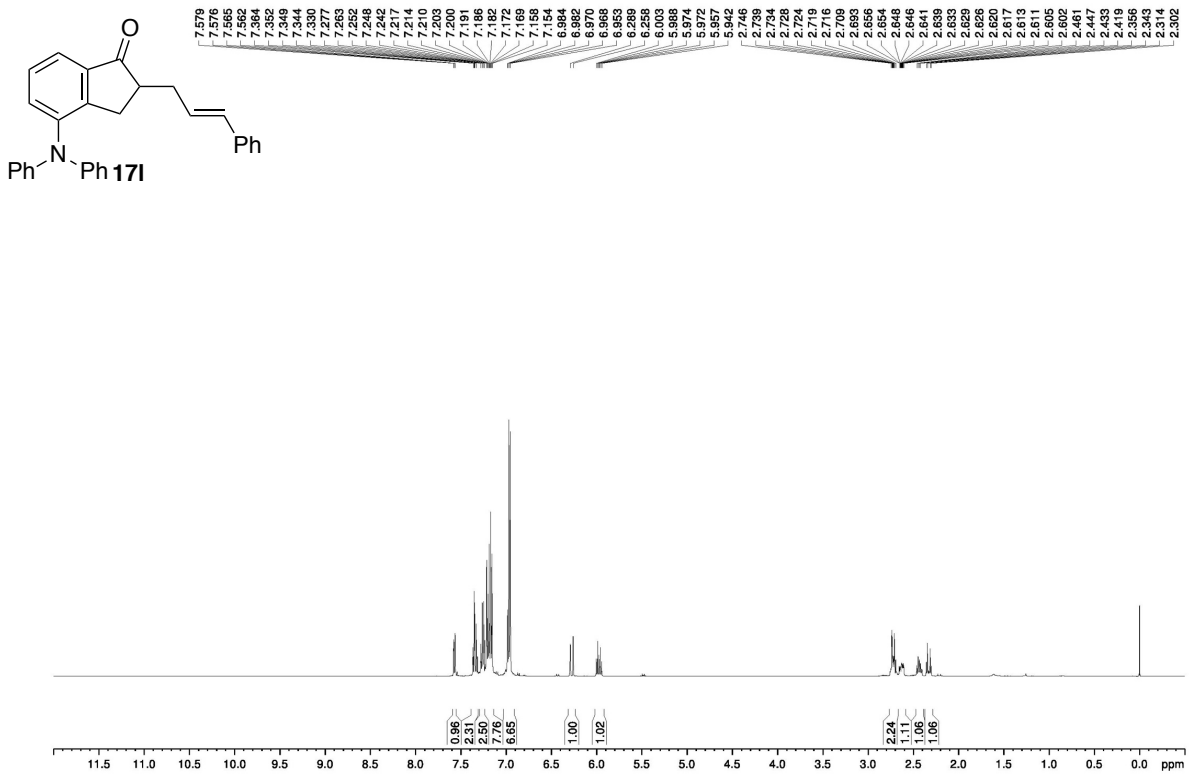
2-Cinnamyl-1-oxo-2,3-dihydro-1*H*-indene-4-carbonitrile, ^{1}H NMR (500 MHz, $CDCl_3$)



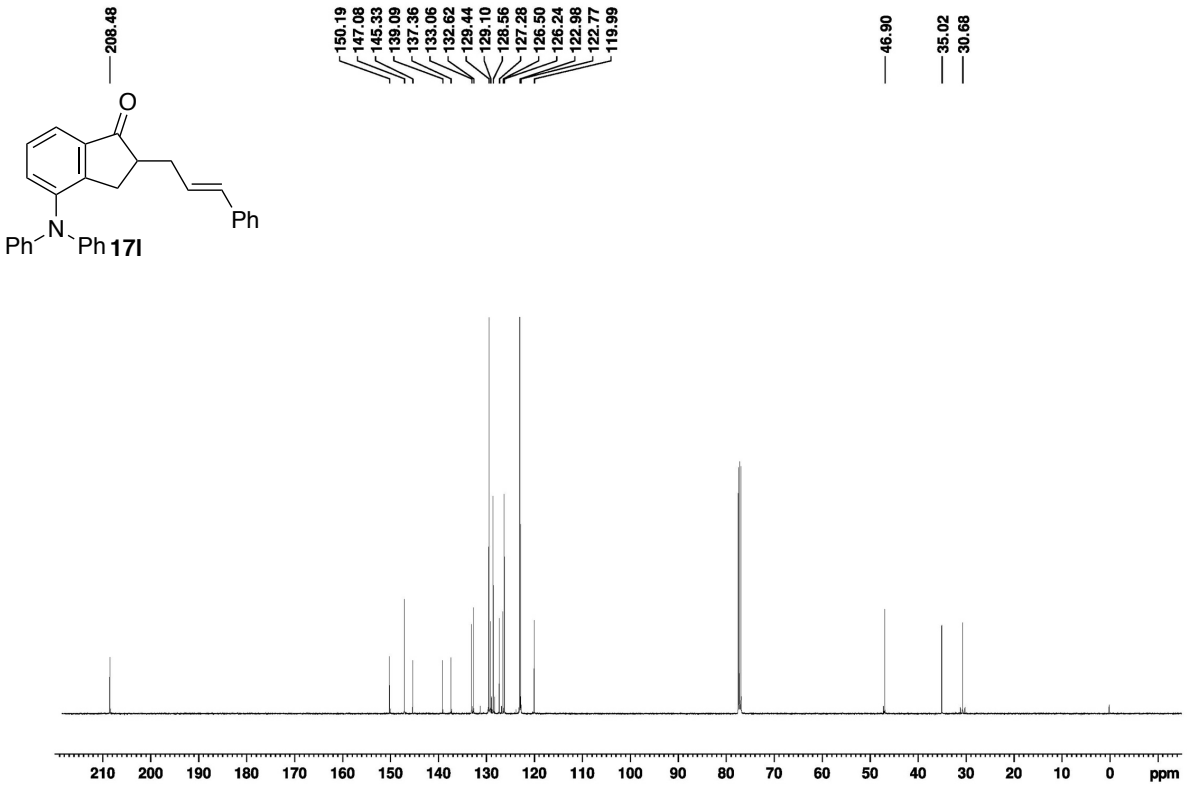
2-Cinnamyl-1-oxo-2,3-dihydro-1*H*-indene-4-carbonitrile, ^{13}C NMR (126 MHz, $CDCl_3$)



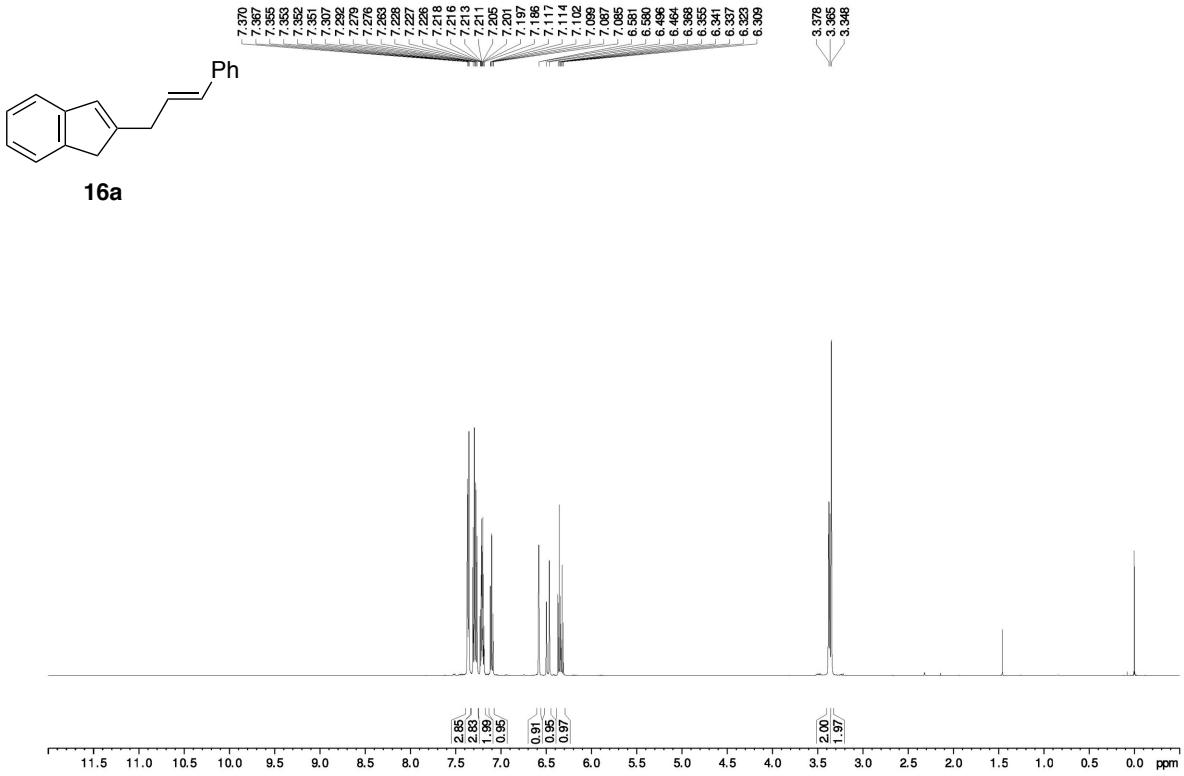
17l, ^{1}H NMR (500 MHz, $CDCl_3$)



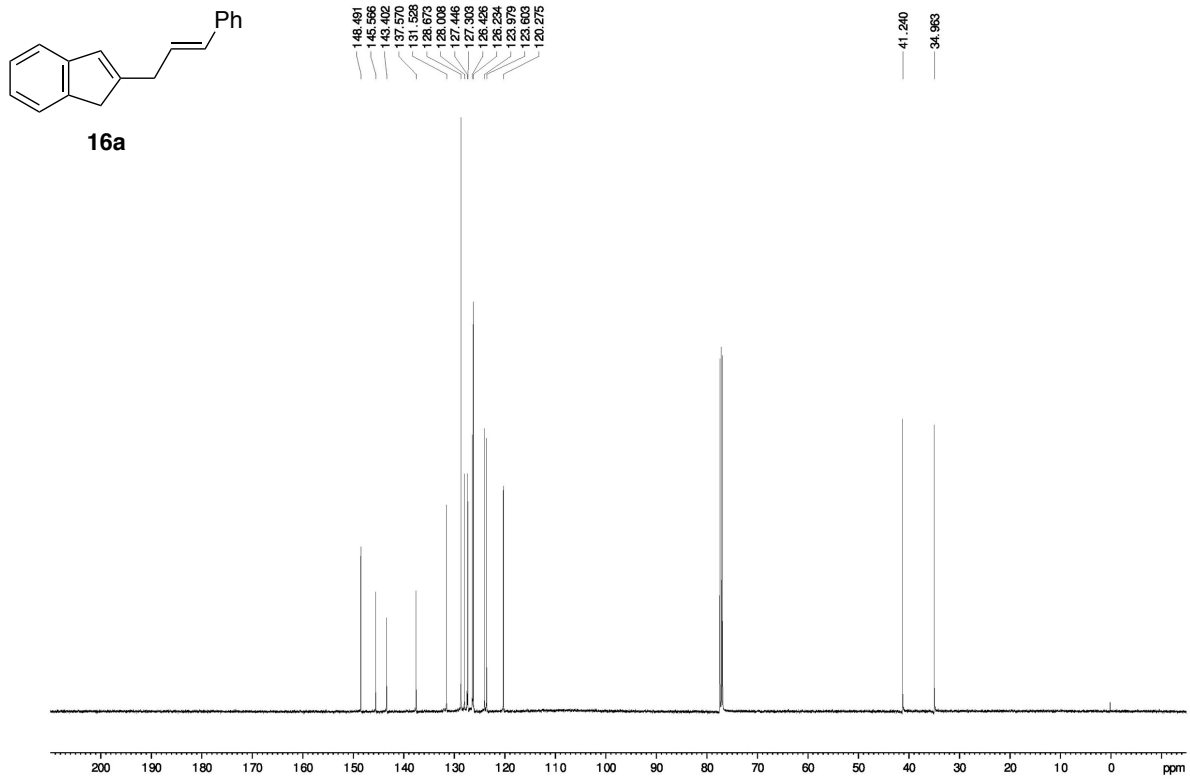
17l, ^{13}C NMR (126 MHz, $CDCl_3$)



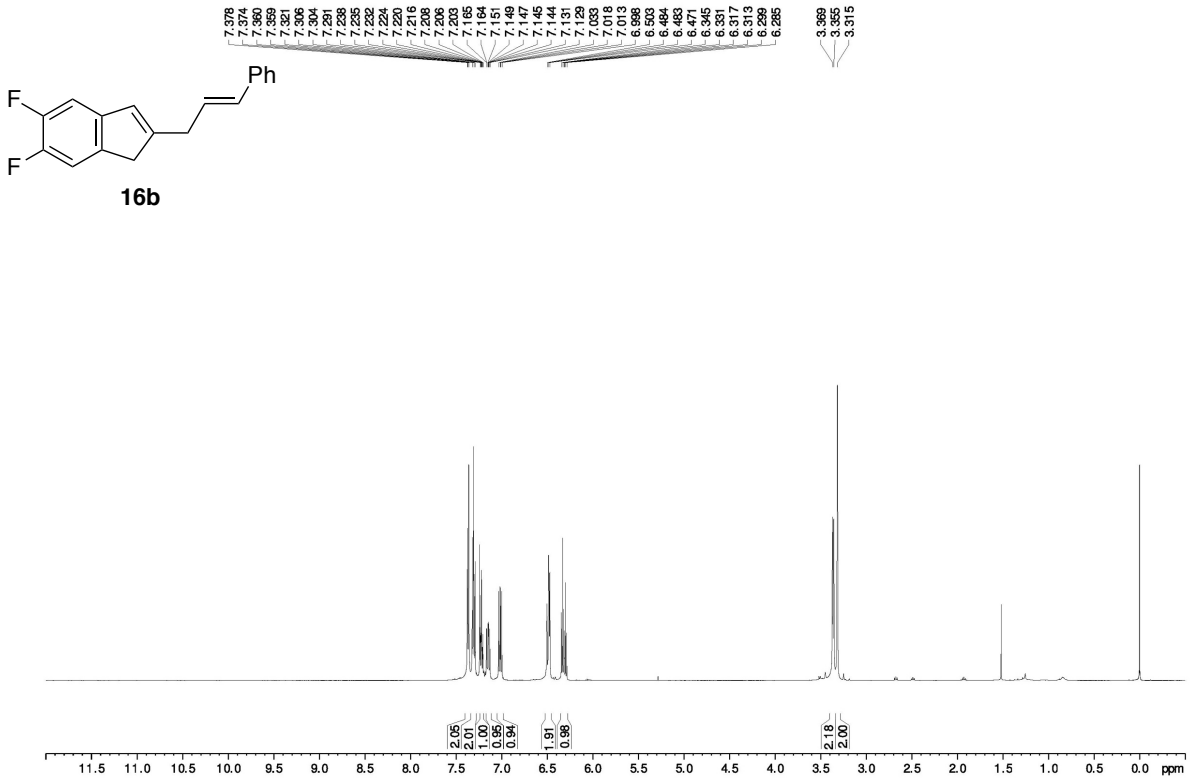
16a, ^{1}H NMR (500 MHz, $CDCl_3$)



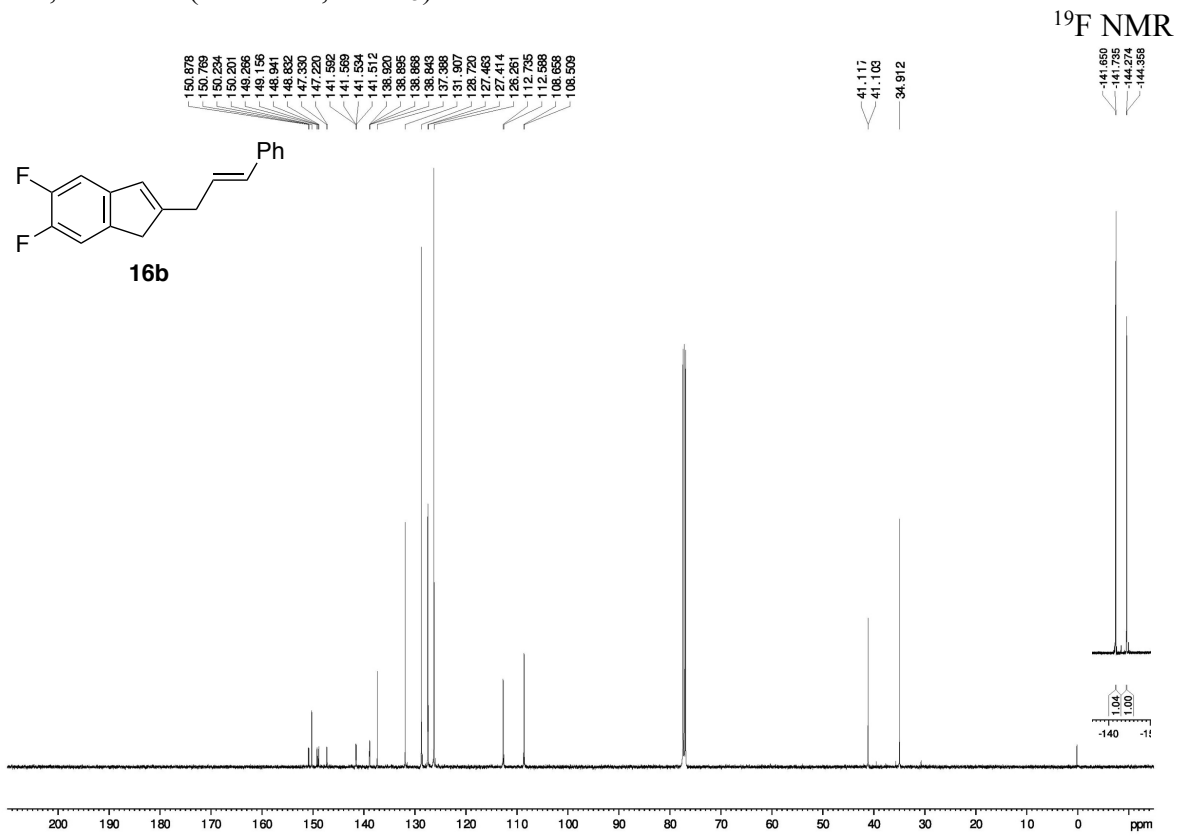
16a, ^{13}C NMR (126 MHz, $CDCl_3$)



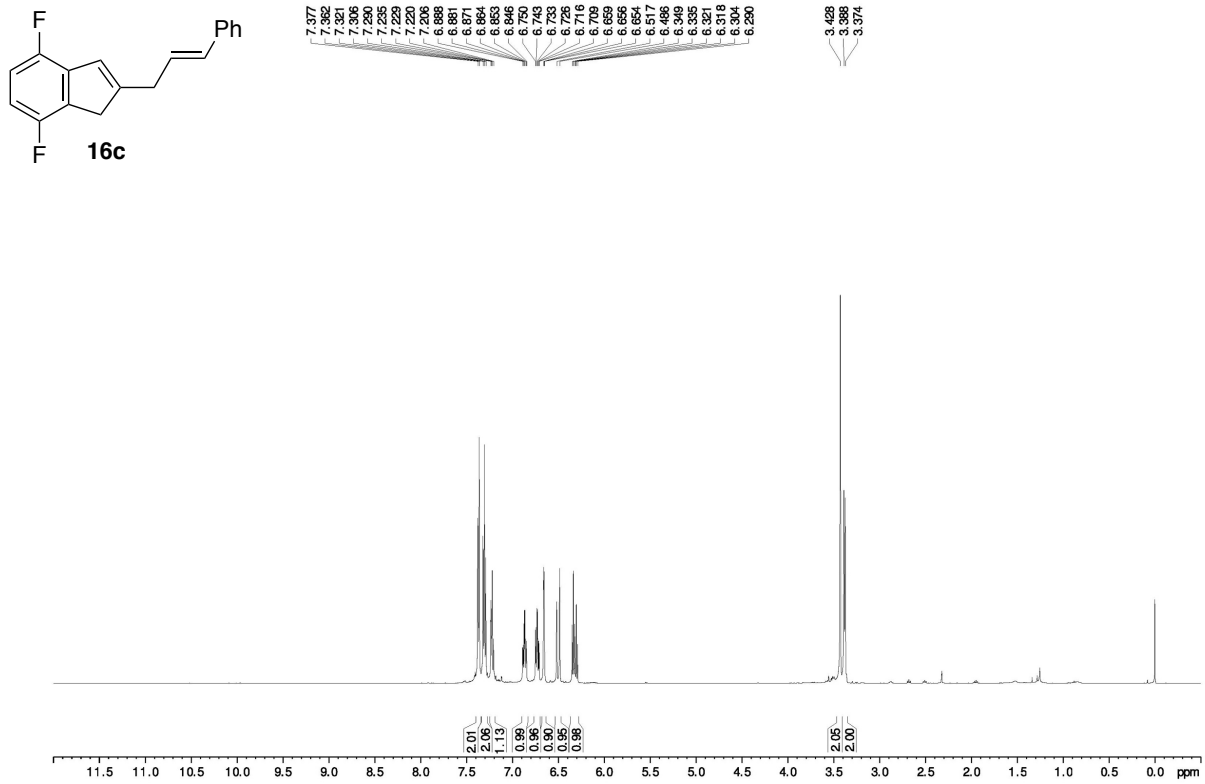
16b, ^{1}H NMR (500 MHz, $CDCl_3$)



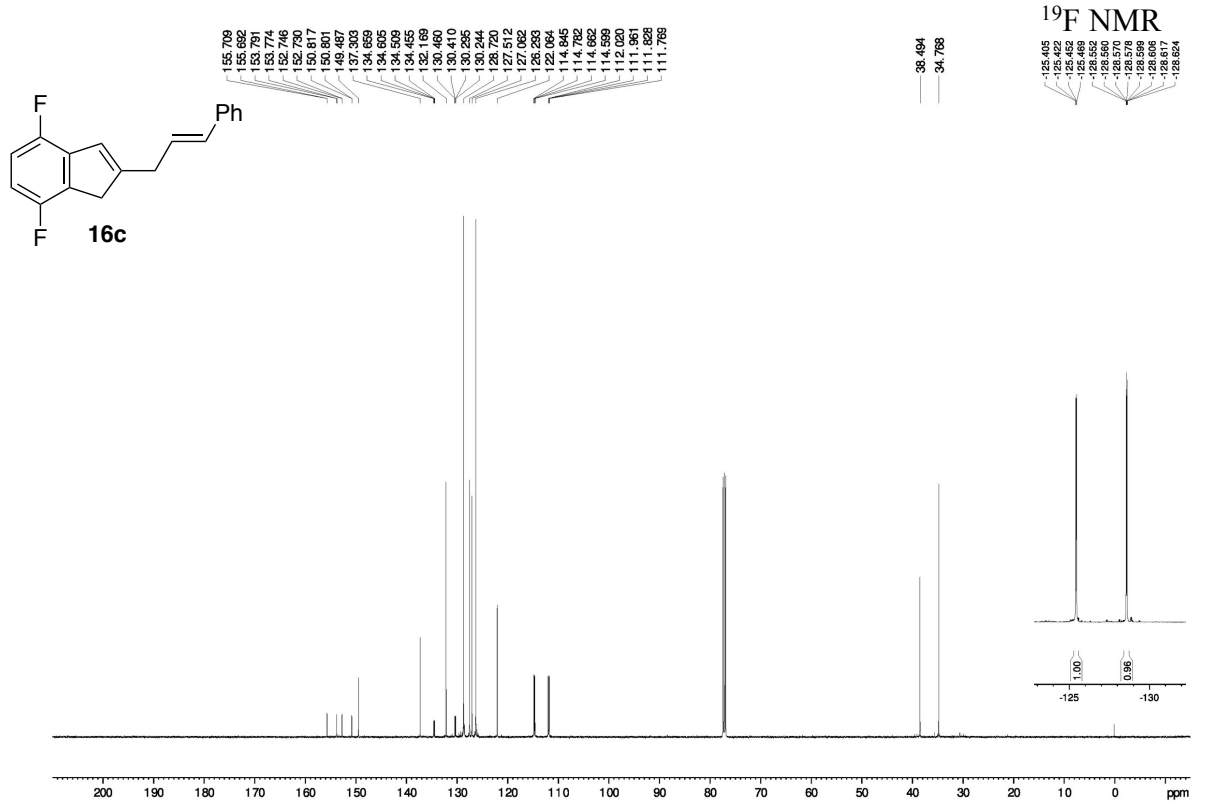
16b,^{13}C NMR (126 MHz, $CDCl_3$)



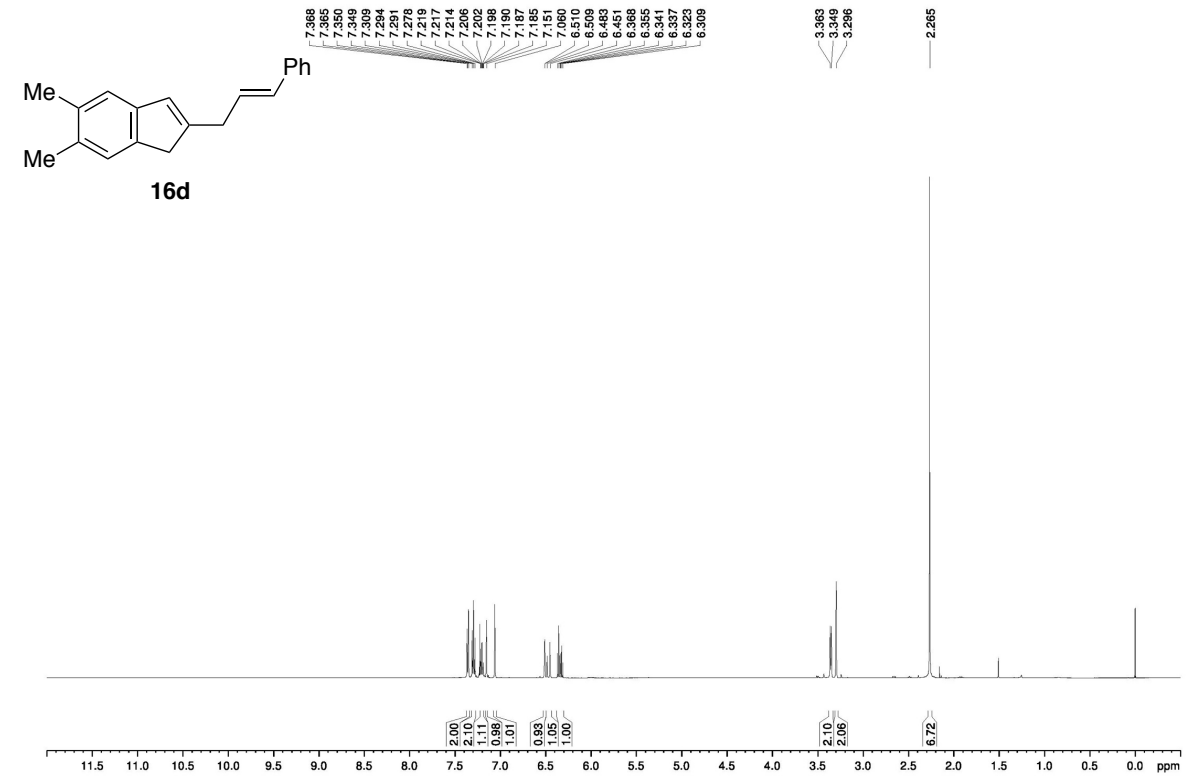
16c, ^{1}H NMR (500 MHz, $CDCl_3$)



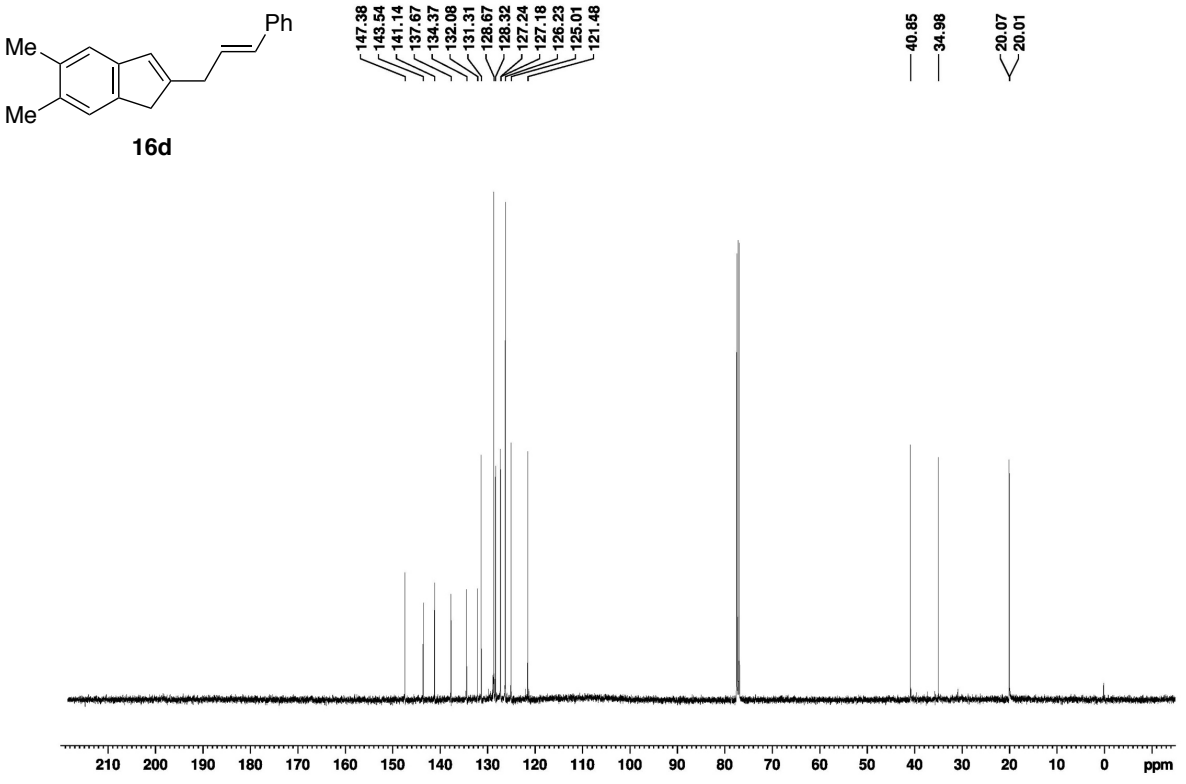
16c,^{13}C NMR (126 MHz, $CDCl_3$)



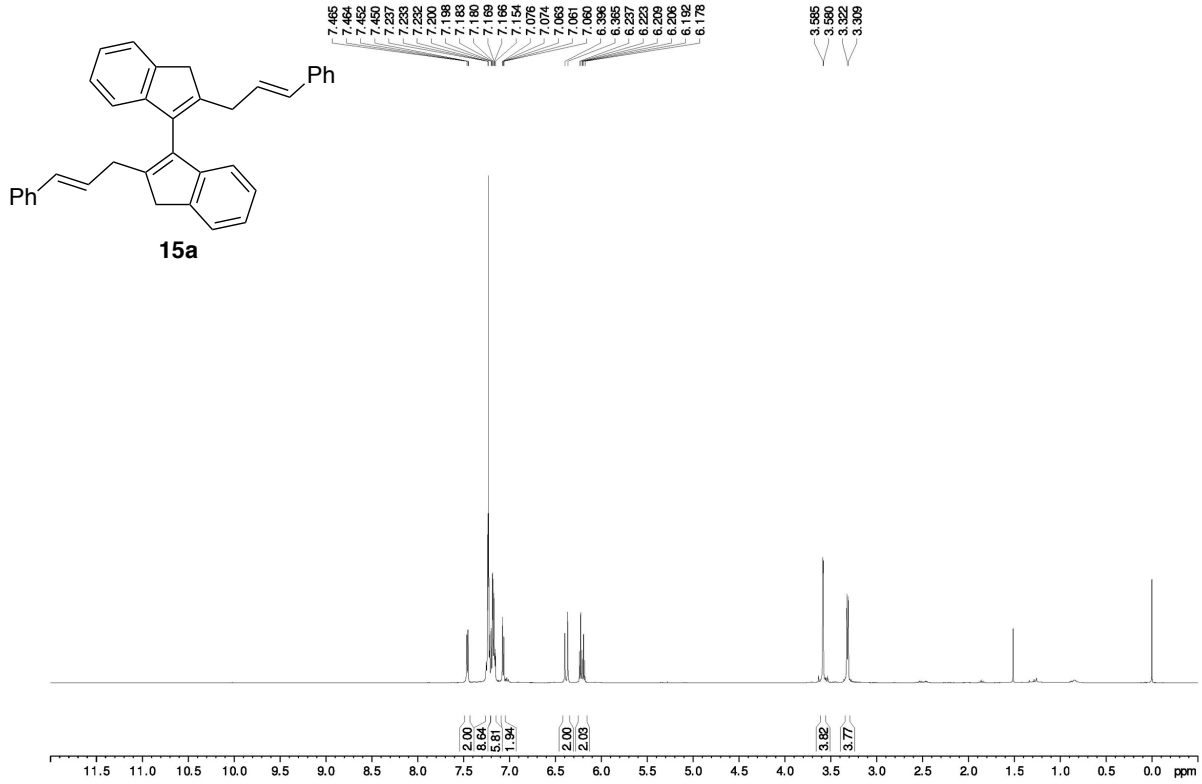
16d, ^{1}H NMR (500 MHz, $CDCl_3$)



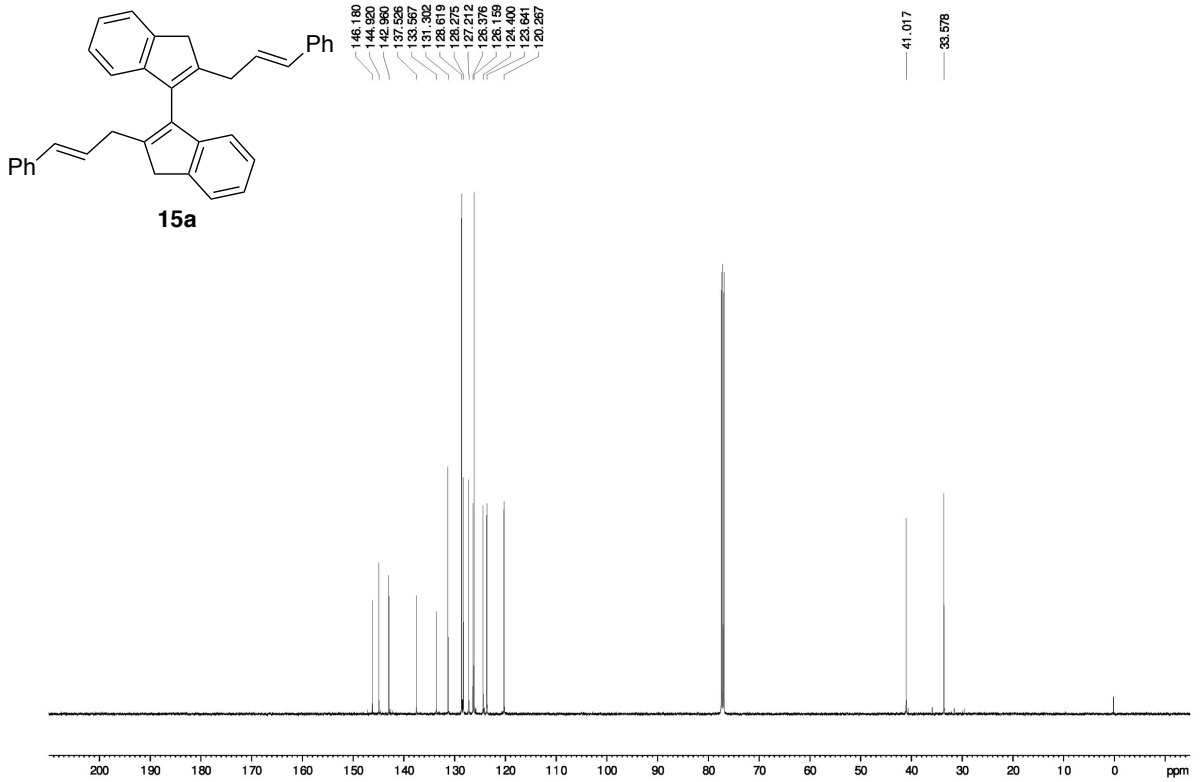
16d,^{13}C NMR (126 MHz, $CDCl_3$)



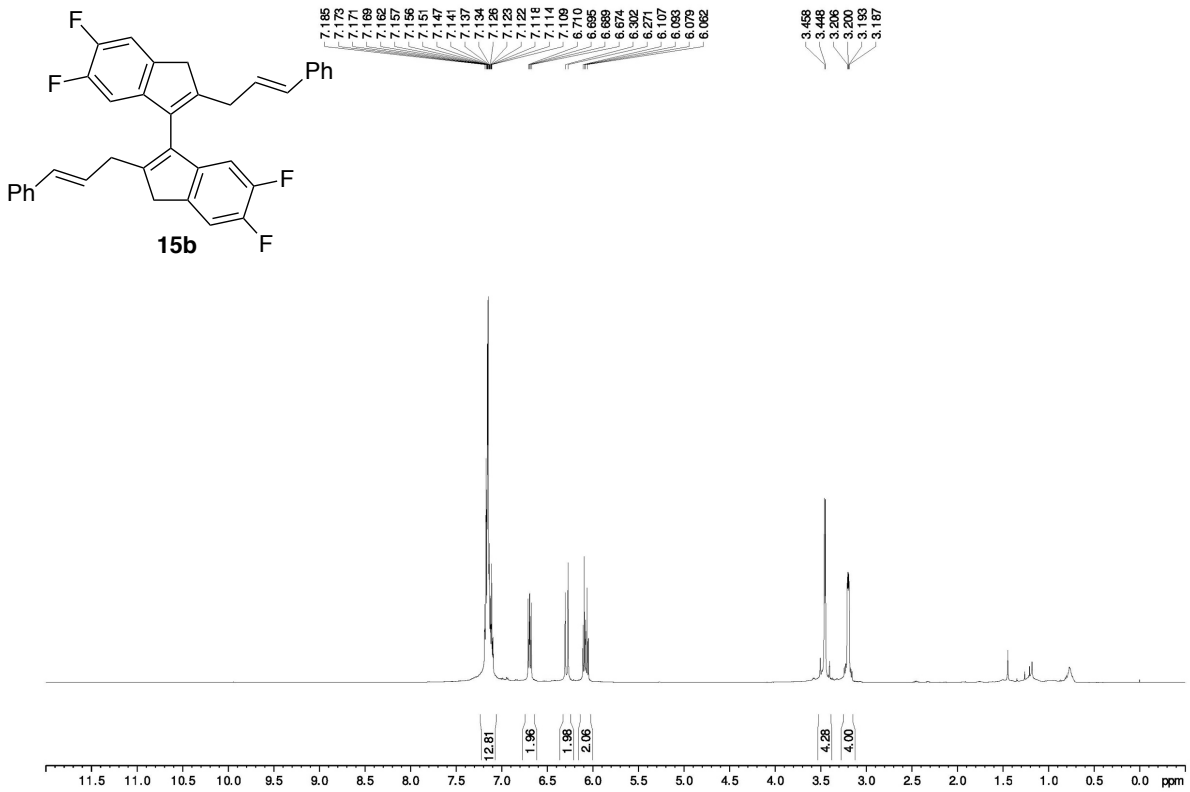
15a, ^{1}H NMR (500 MHz, $CDCl_3$)



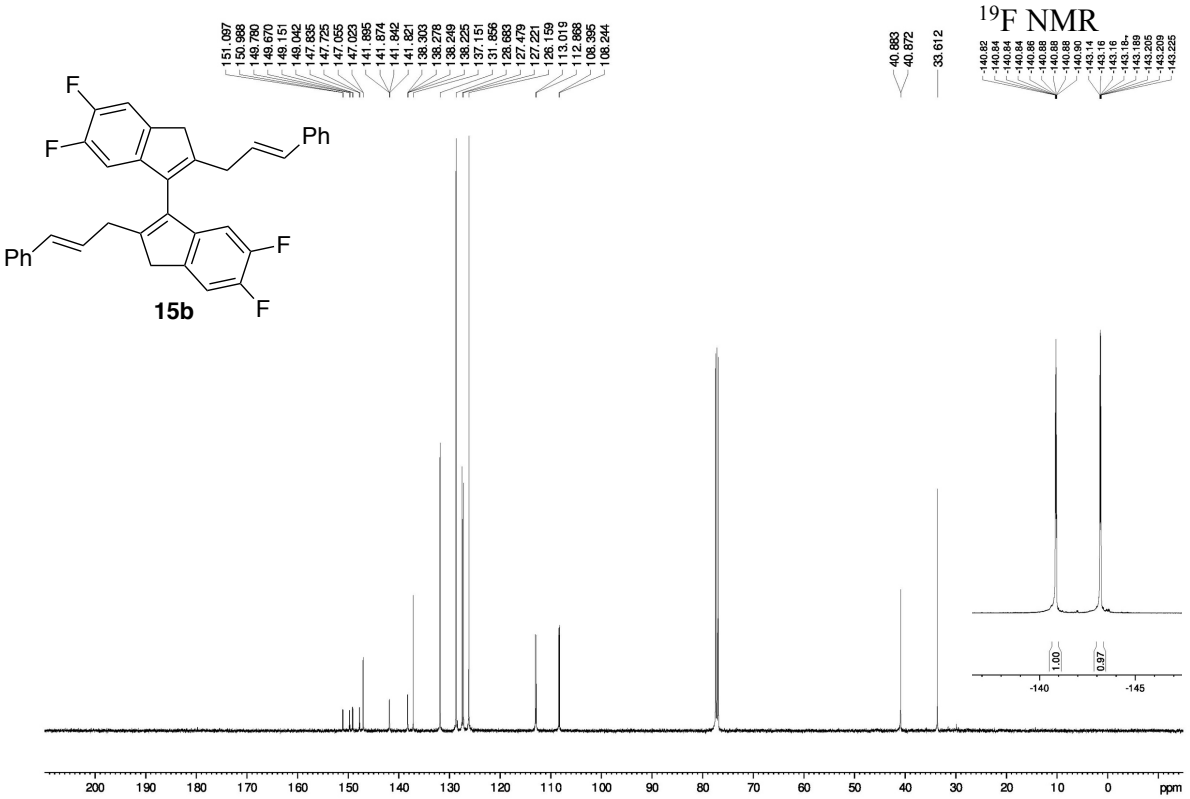
15a,^{13}C NMR (126 MHz, $CDCl_3$)



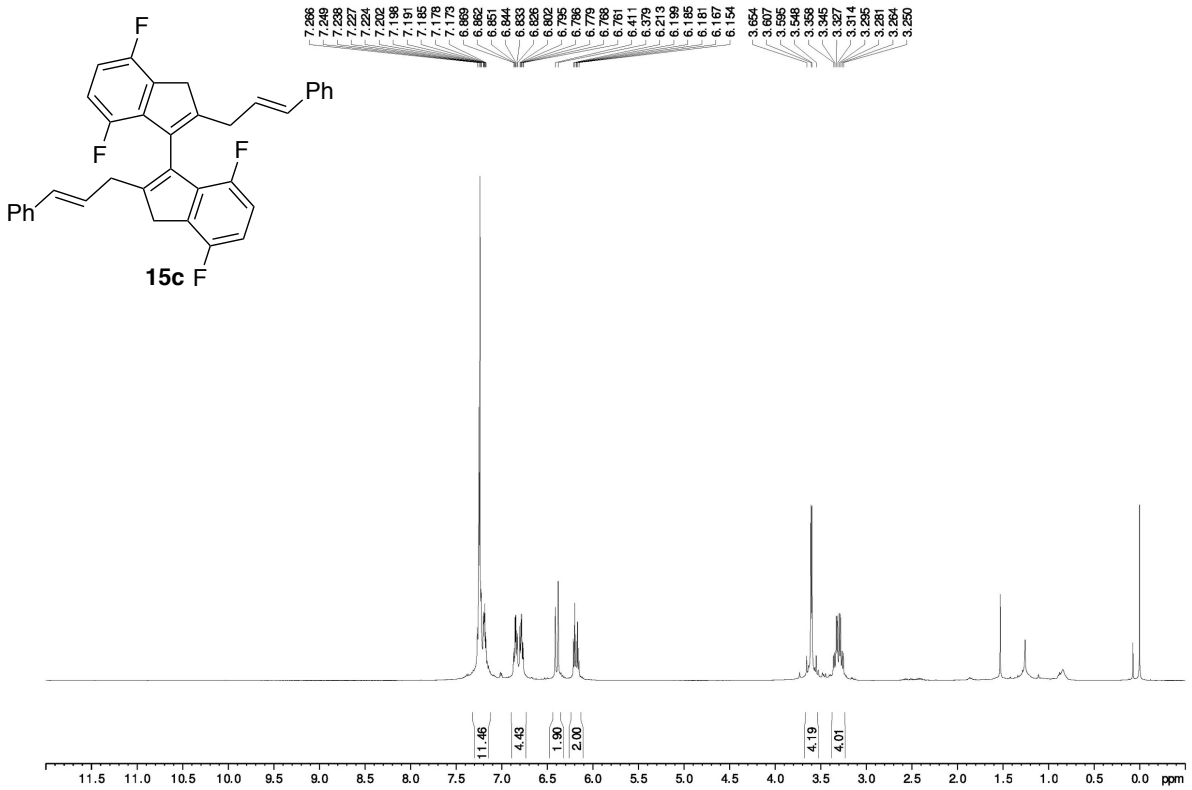
15b, ^{1}H NMR (500 MHz, $CDCl_3$)



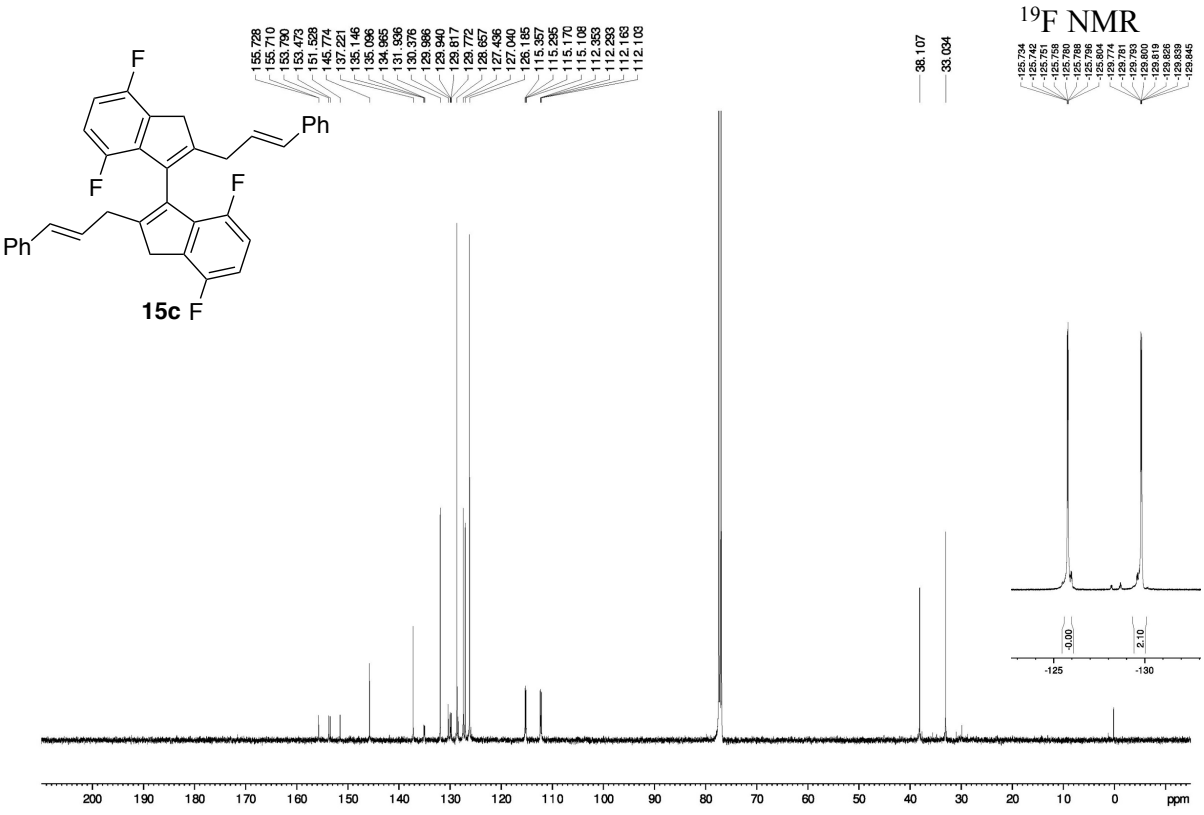
15b,^{13}C NMR (126 MHz, $CDCl_3$)



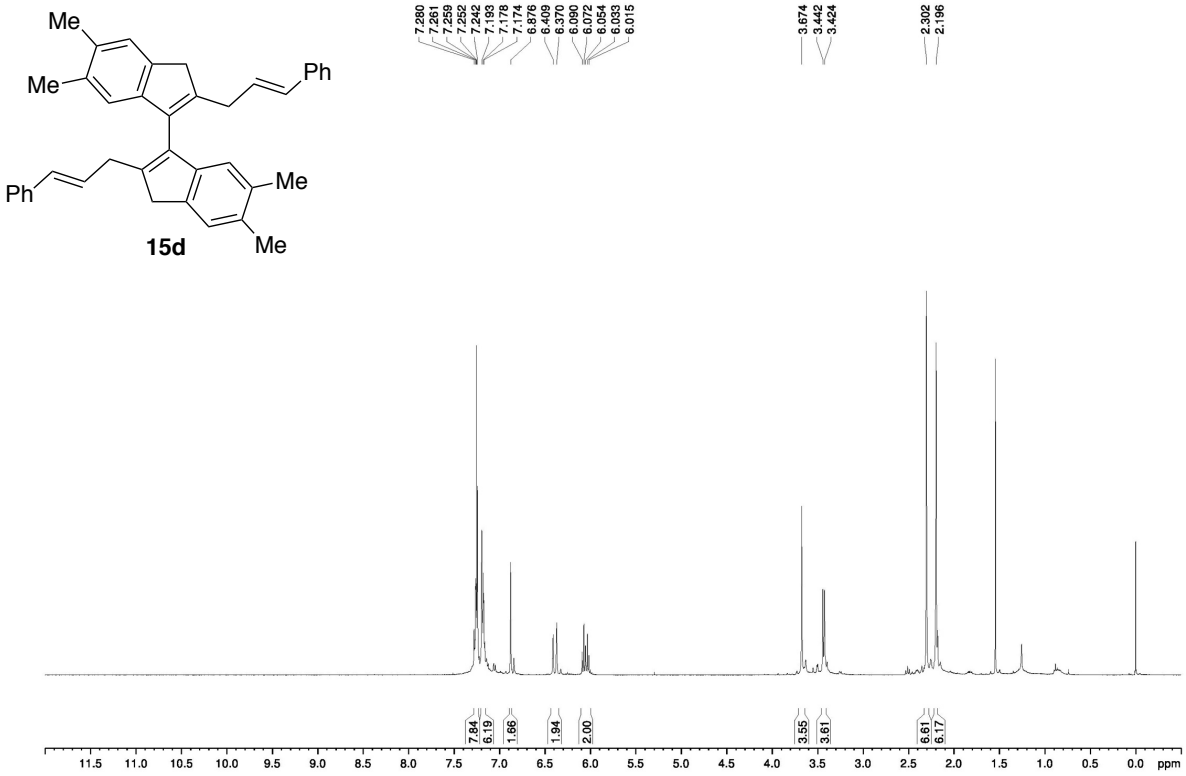
15c, ^{1}H NMR (500 MHz, $CDCl_3$)



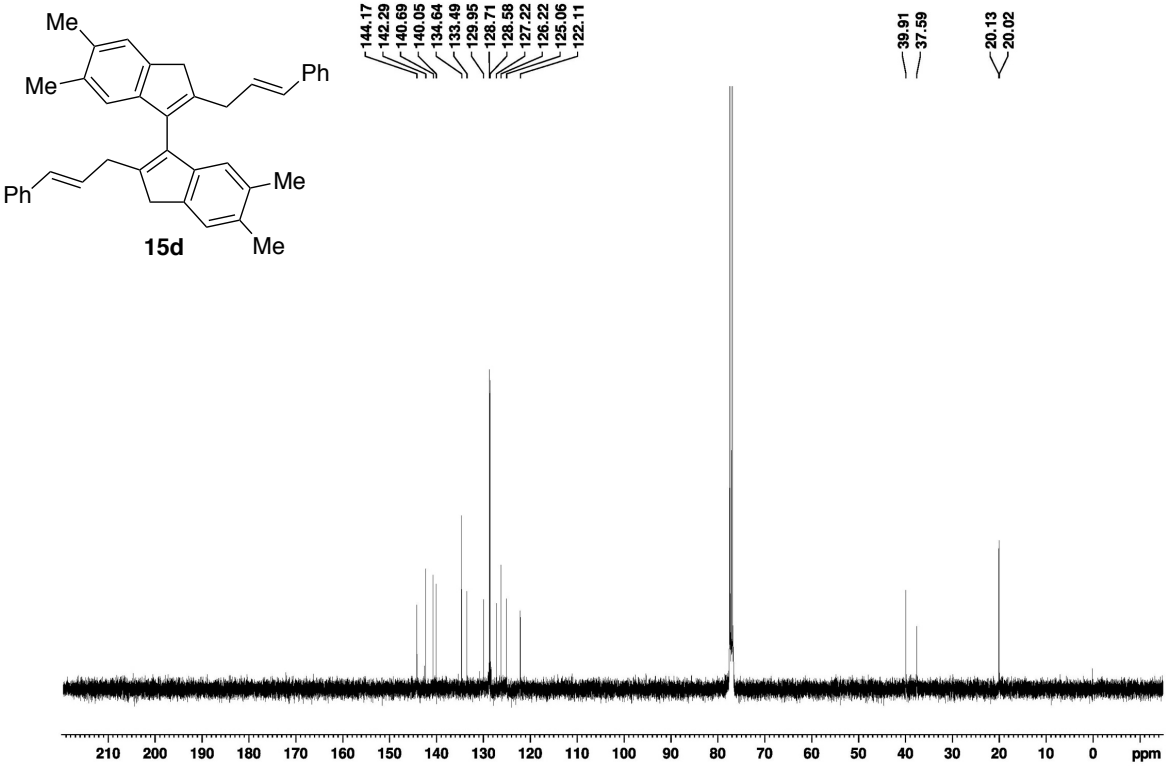
15c,^{13}C NMR (126 MHz, $CDCl_3$)



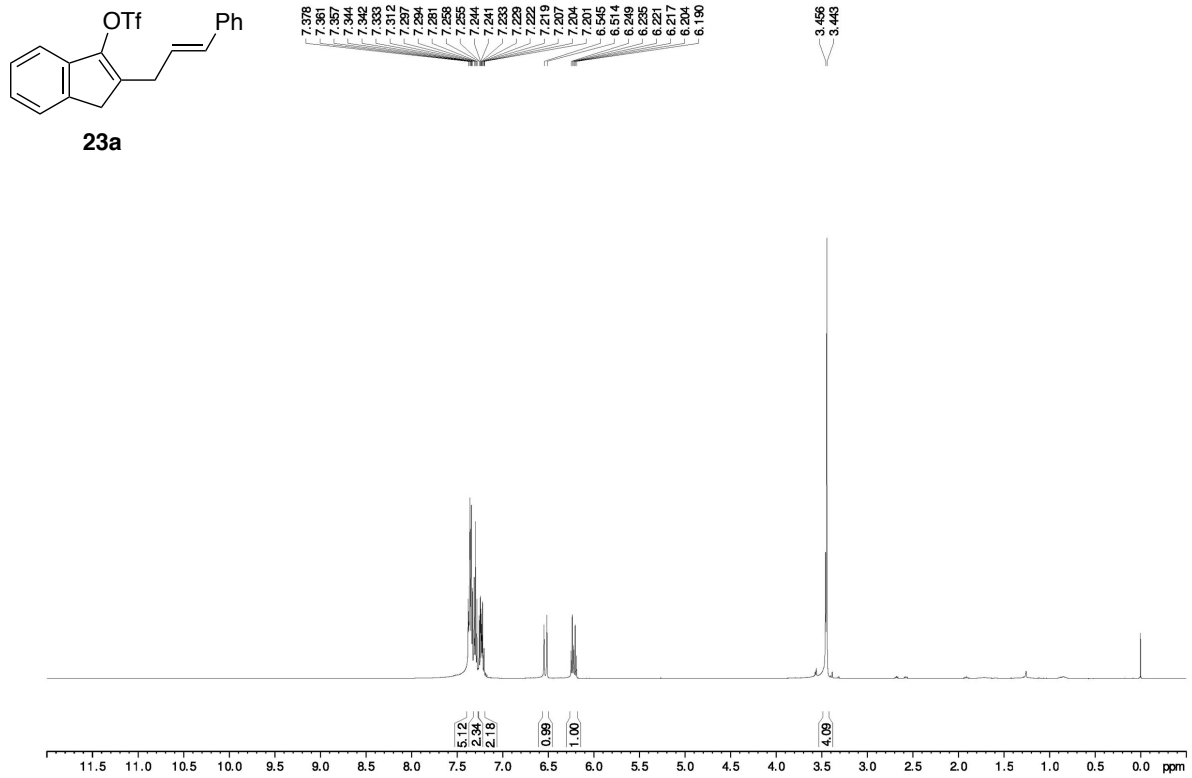
15d, ^{1}H NMR (400 MHz, $CDCl_3$)



15d,^{13}C NMR (101 MHz, $CDCl_3$)

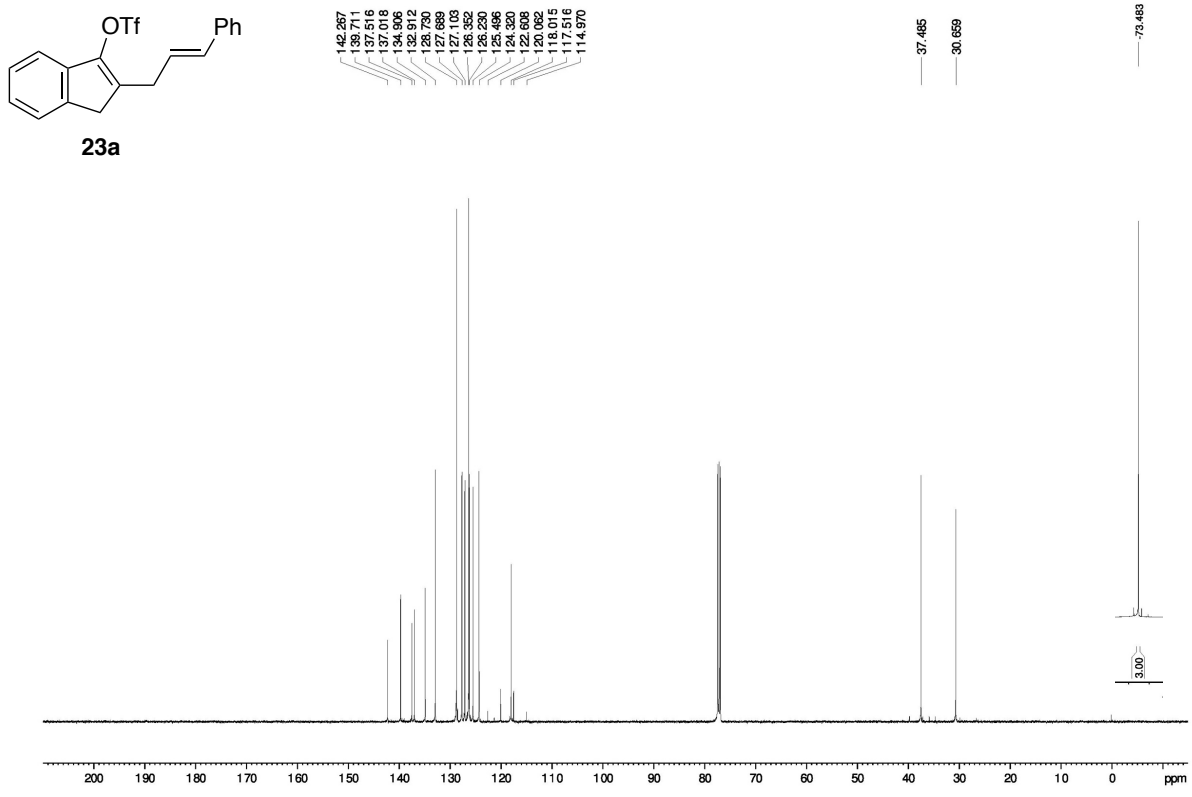


23a, ^{1}H NMR (500 MHz, $CDCl_3$)

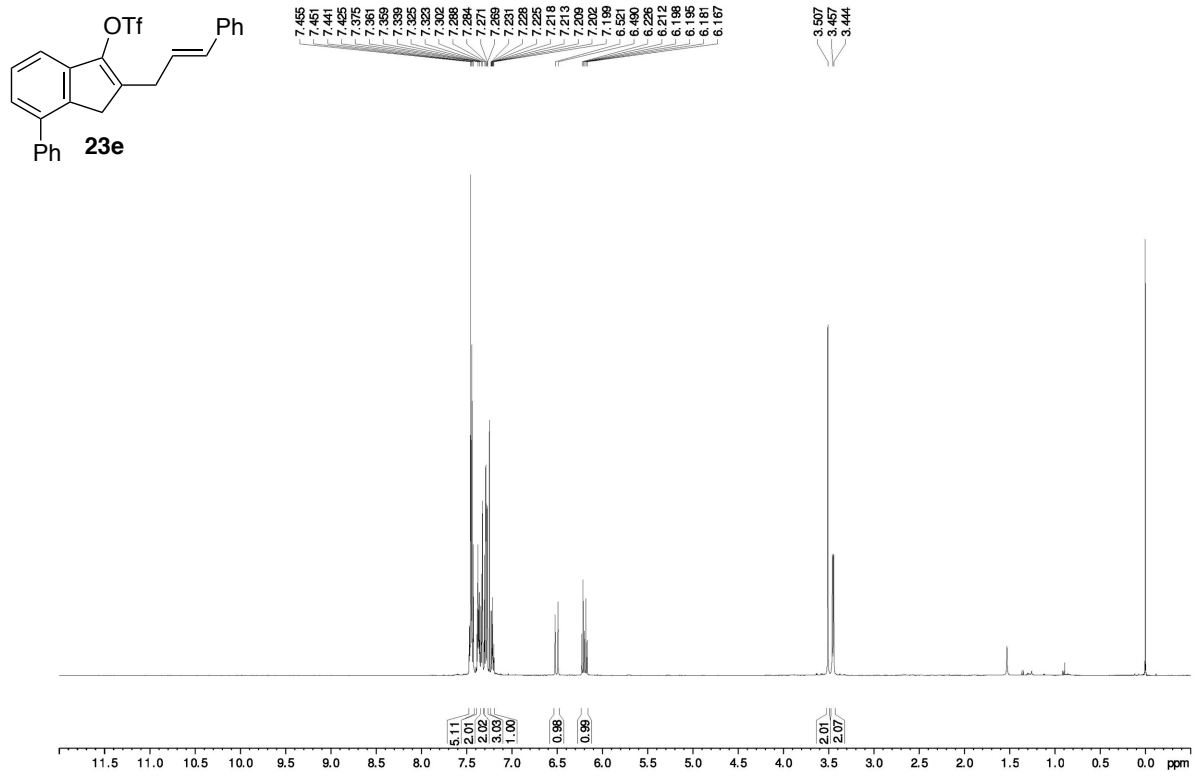


23a, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

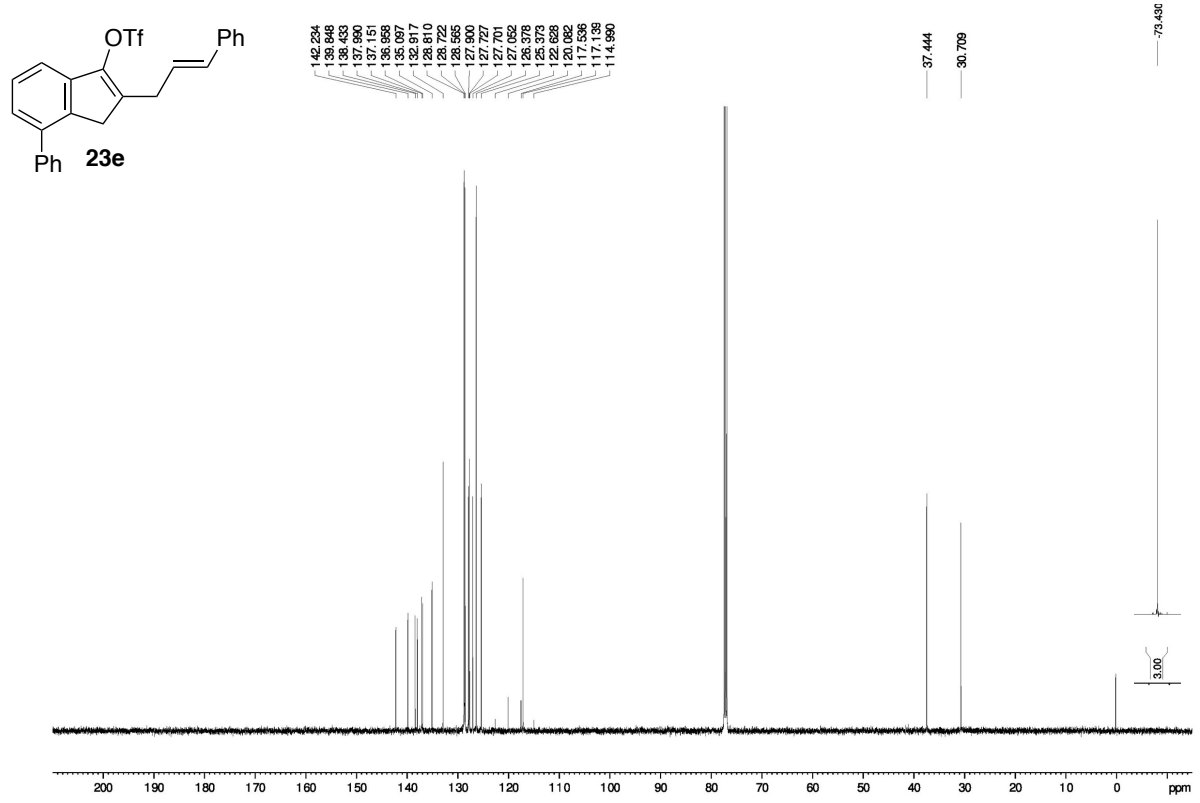


23e, ^{1}H NMR (500 MHz, $CDCl_3$)

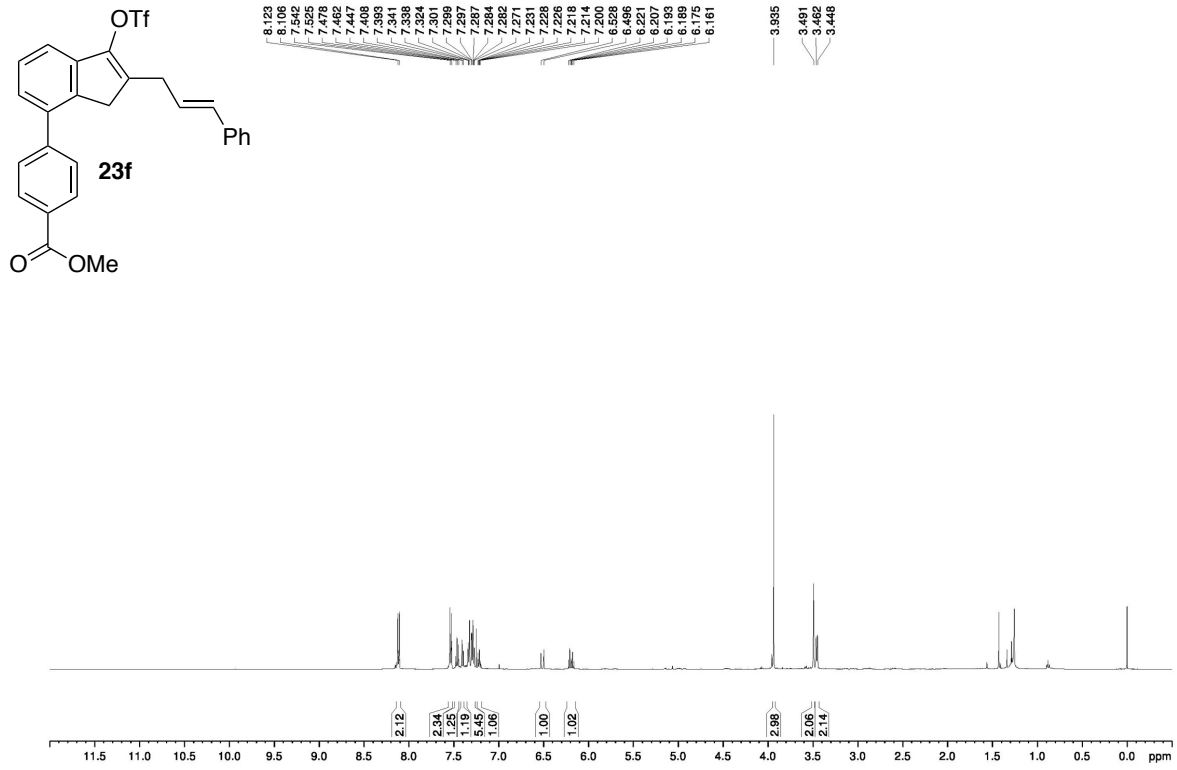


23e, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

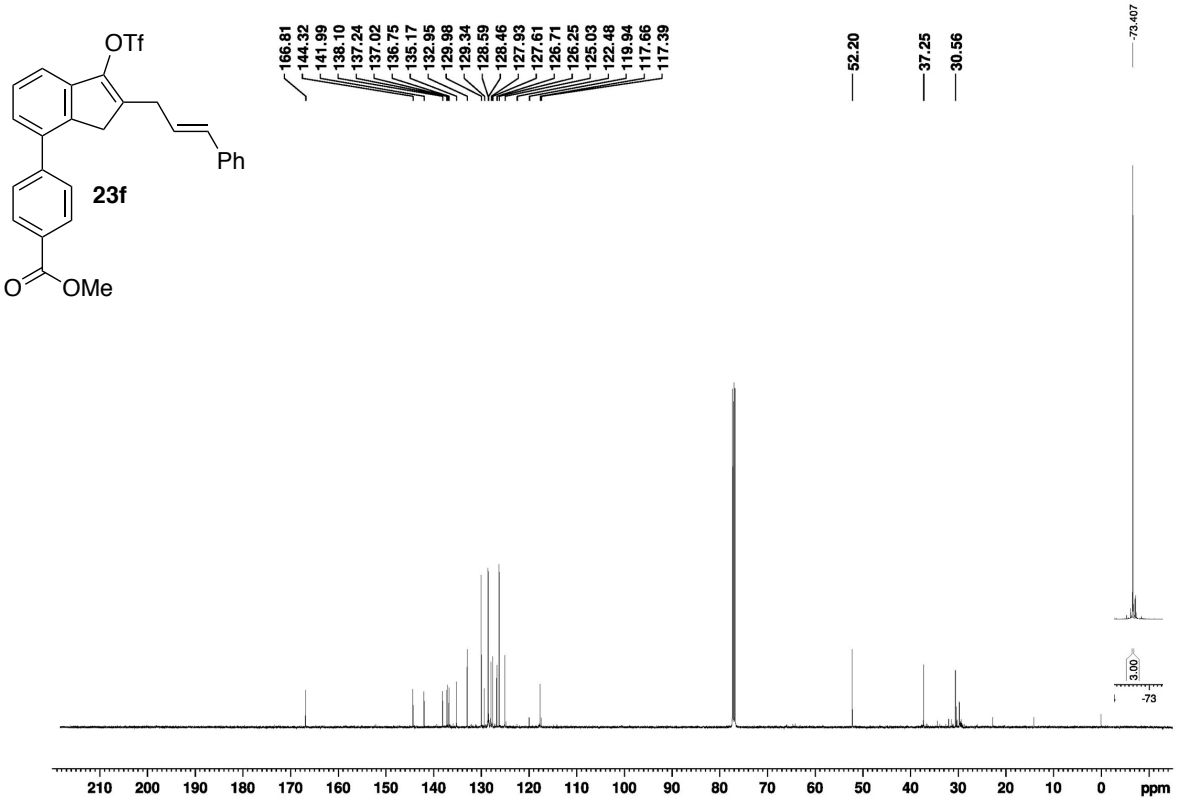


23f, ^{1}H NMR (500 MHz, $CDCl_3$)

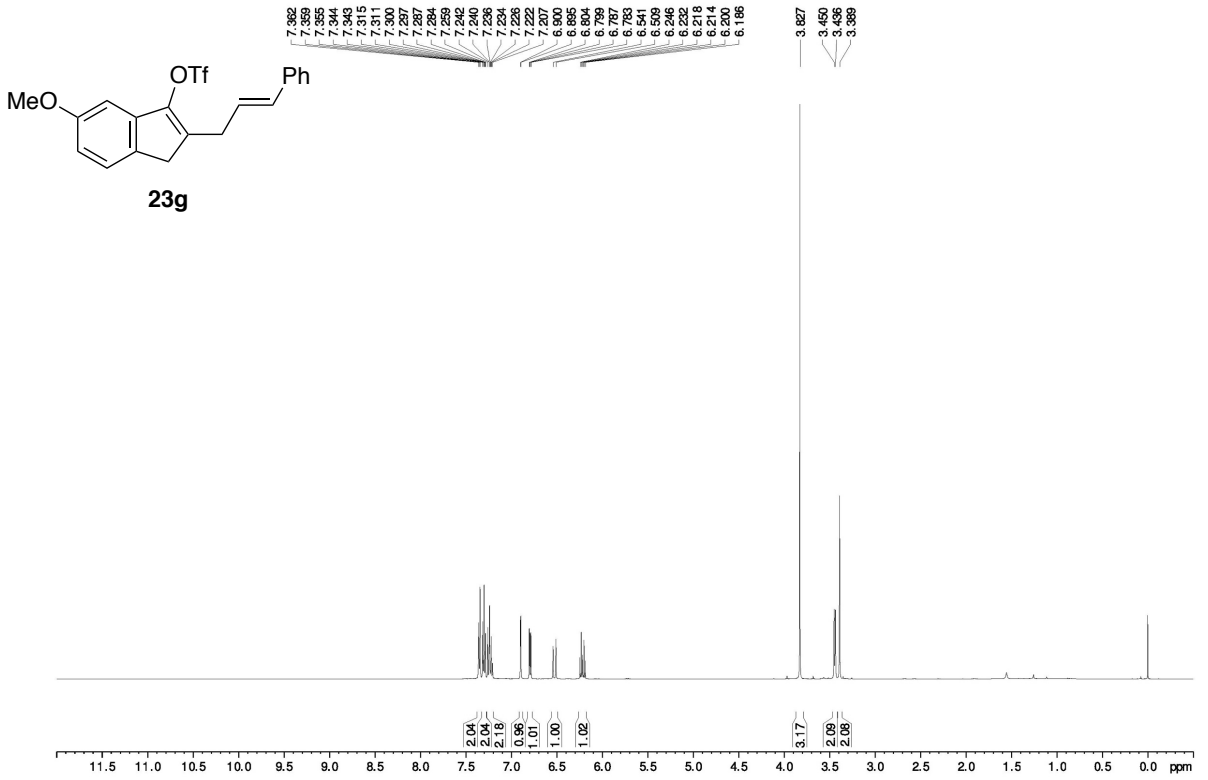


23f, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

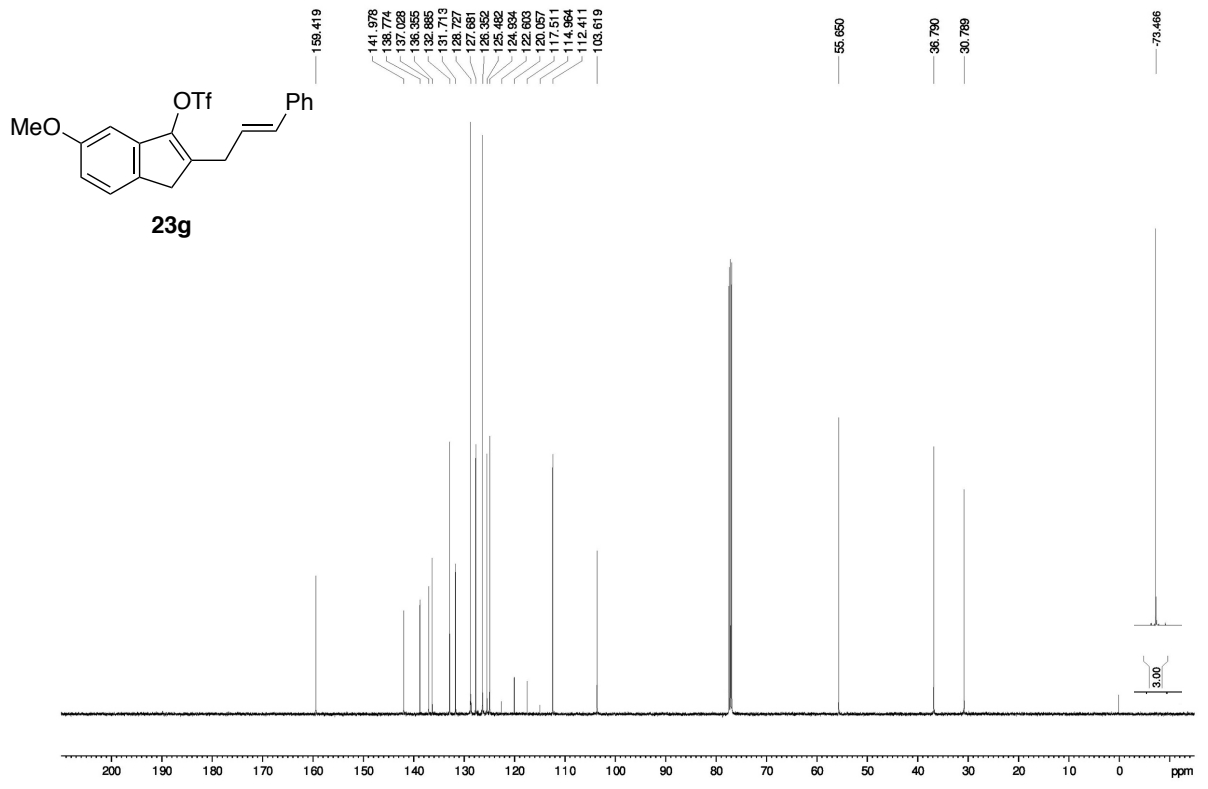


23g, ^{1}H NMR (500 MHz, $CDCl_3$)

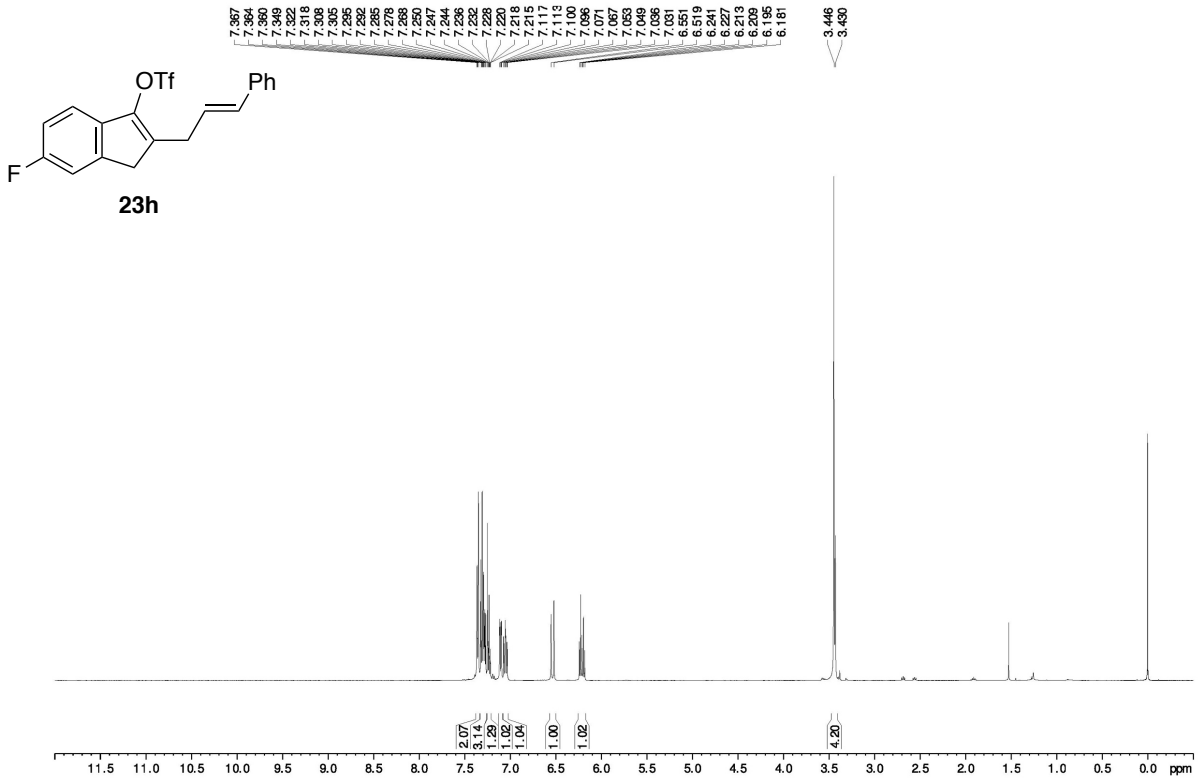


23g, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

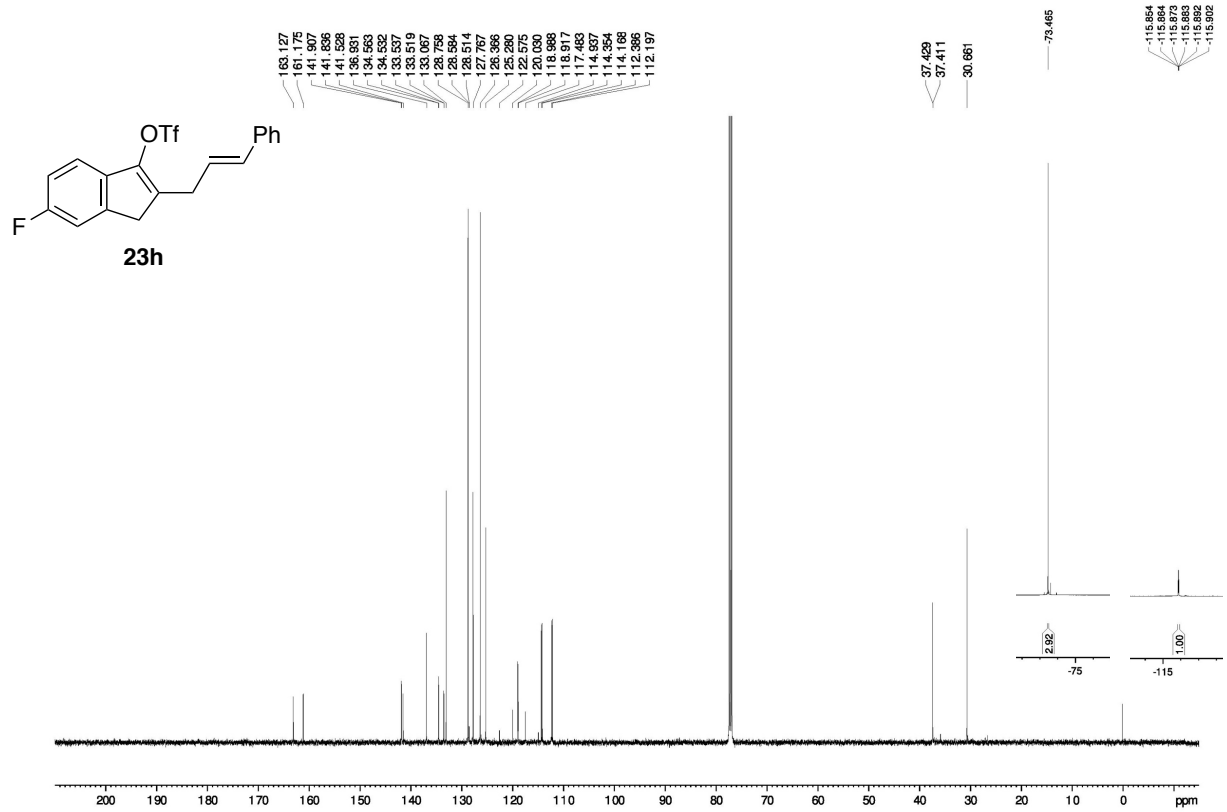


23h, ^{1}H NMR (500 MHz, $CDCl_3$)

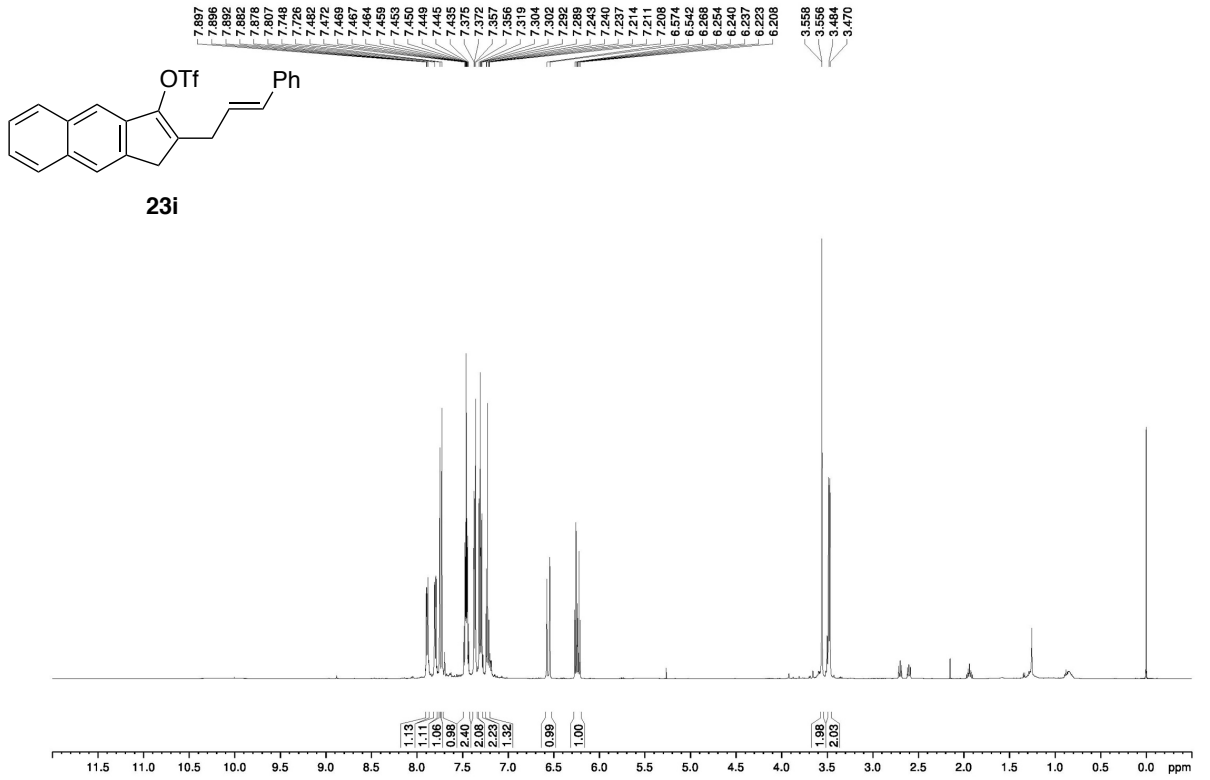


23h, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

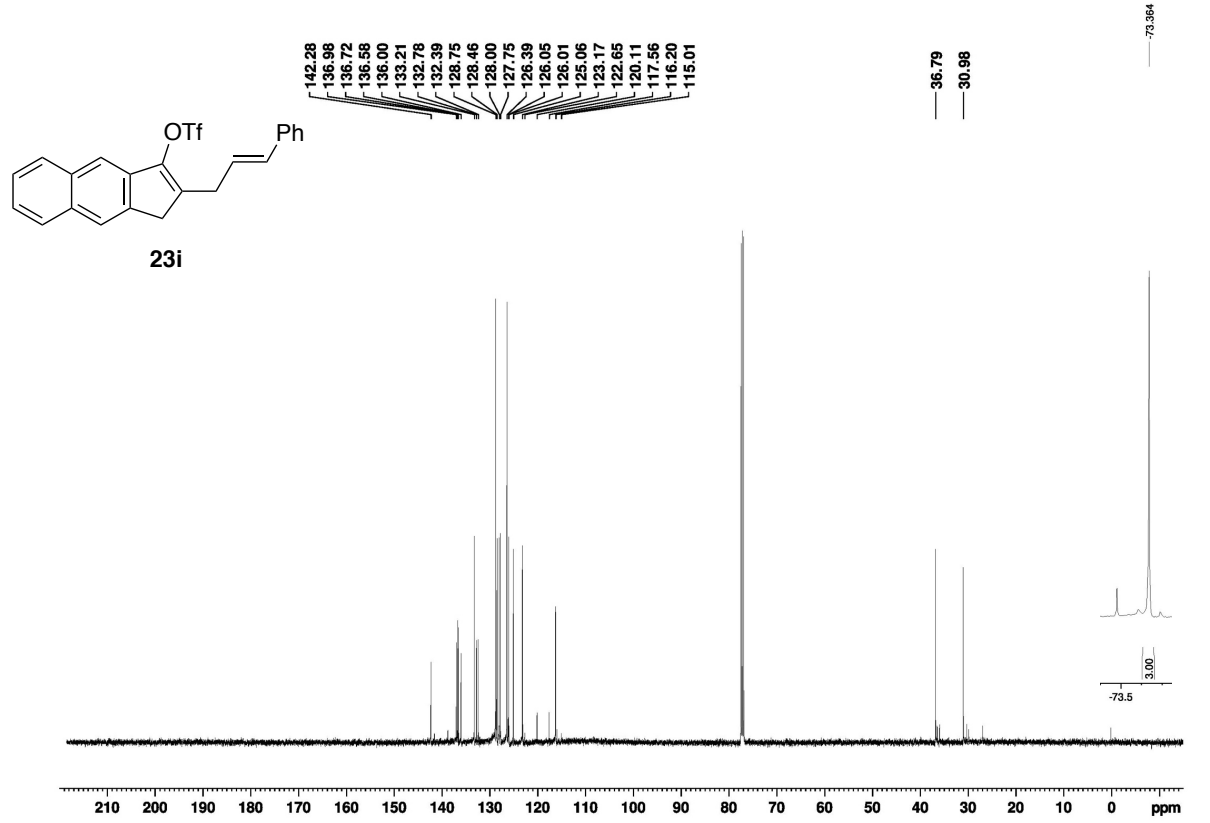


23i, ^{1}H NMR (500 MHz, $CDCl_3$)

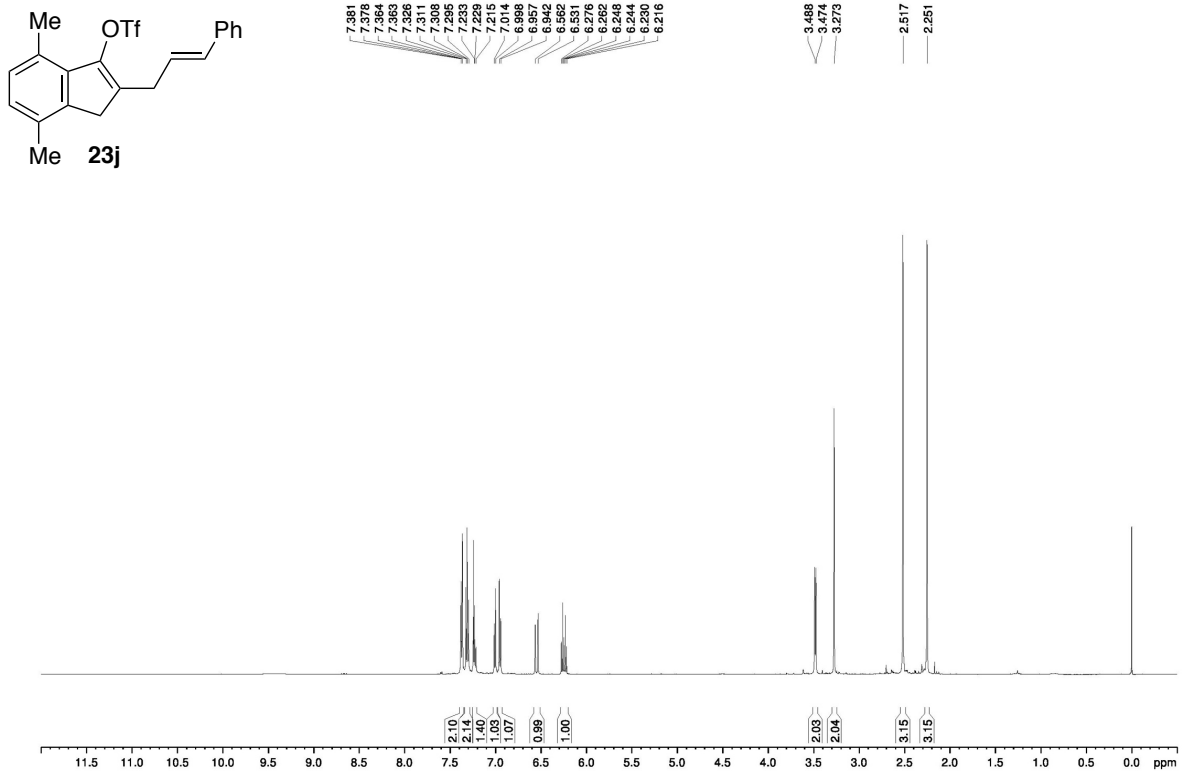


23i, ^{13}C NMR (126 MHz, $CDCl_3$)

^{19}F NMR

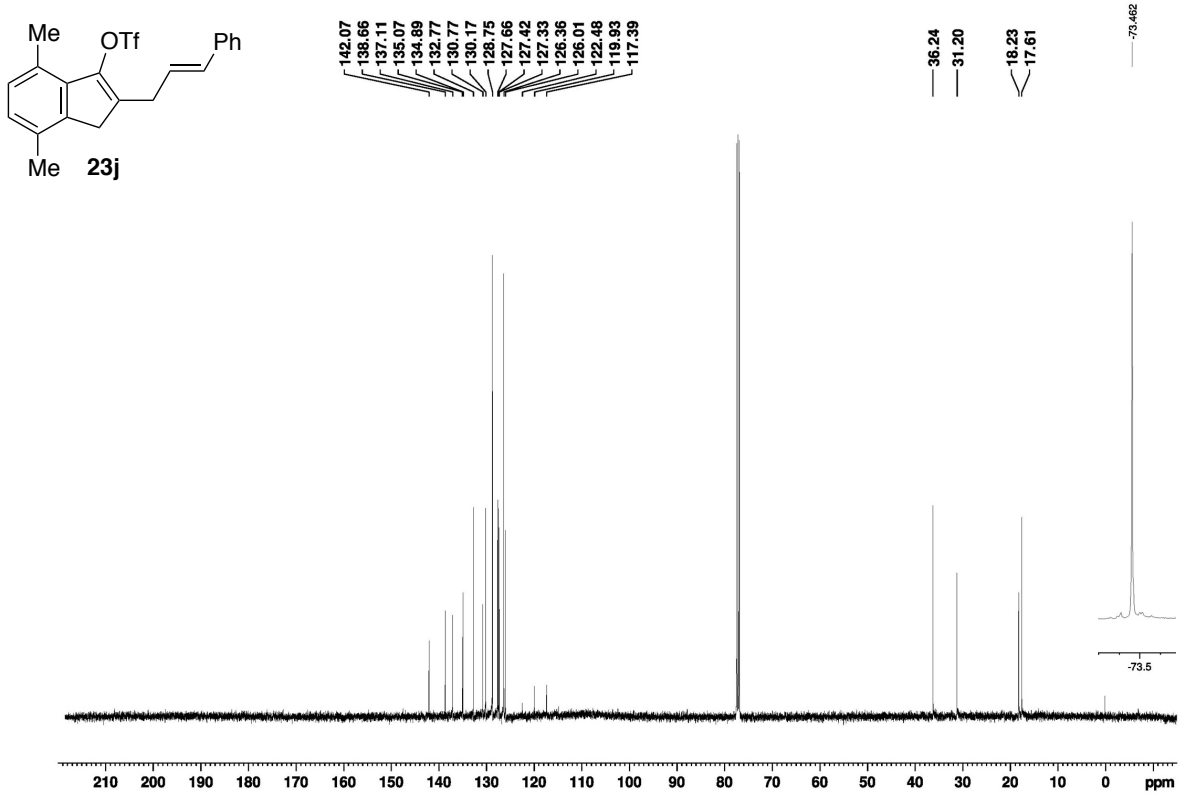


23j, ^{1}H NMR (500 MHz, $CDCl_3$)

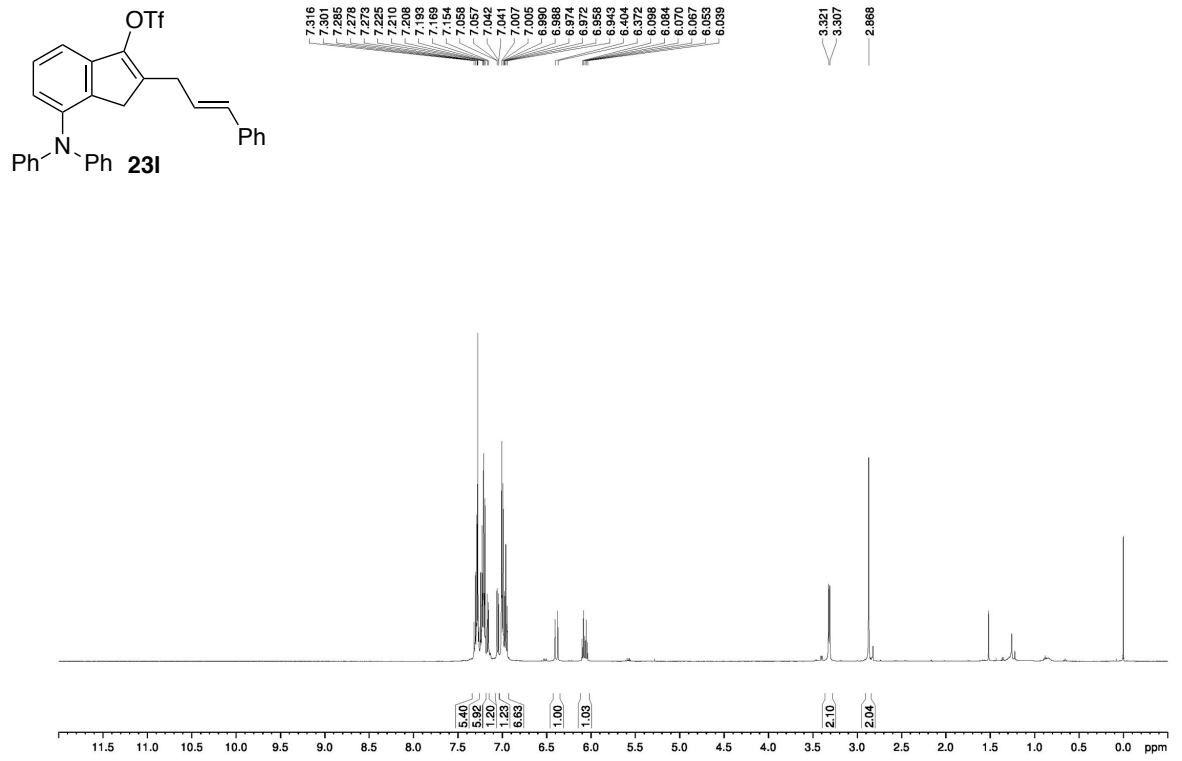


23j, ^{13}C NMR (126 MHz, $CDCl_3$)

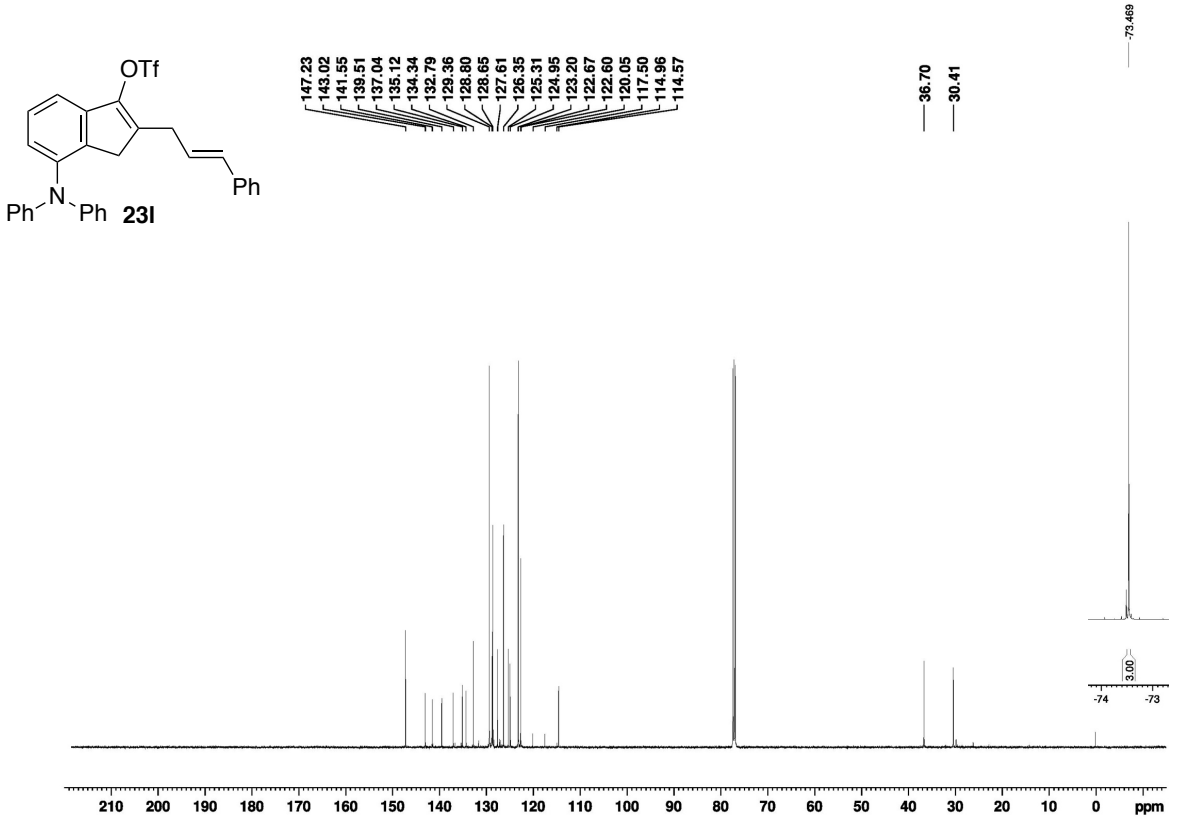
^{19}F NMR



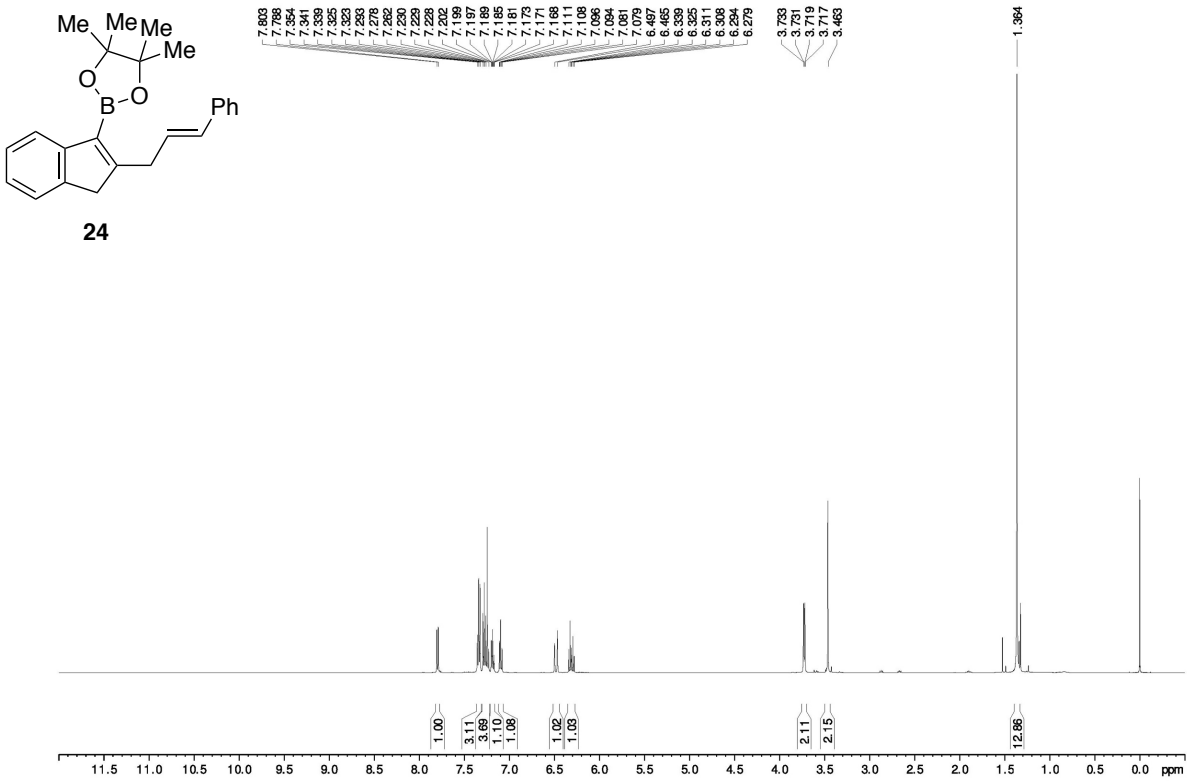
23l, ^{1}H NMR (500 MHz, $CDCl_3$)



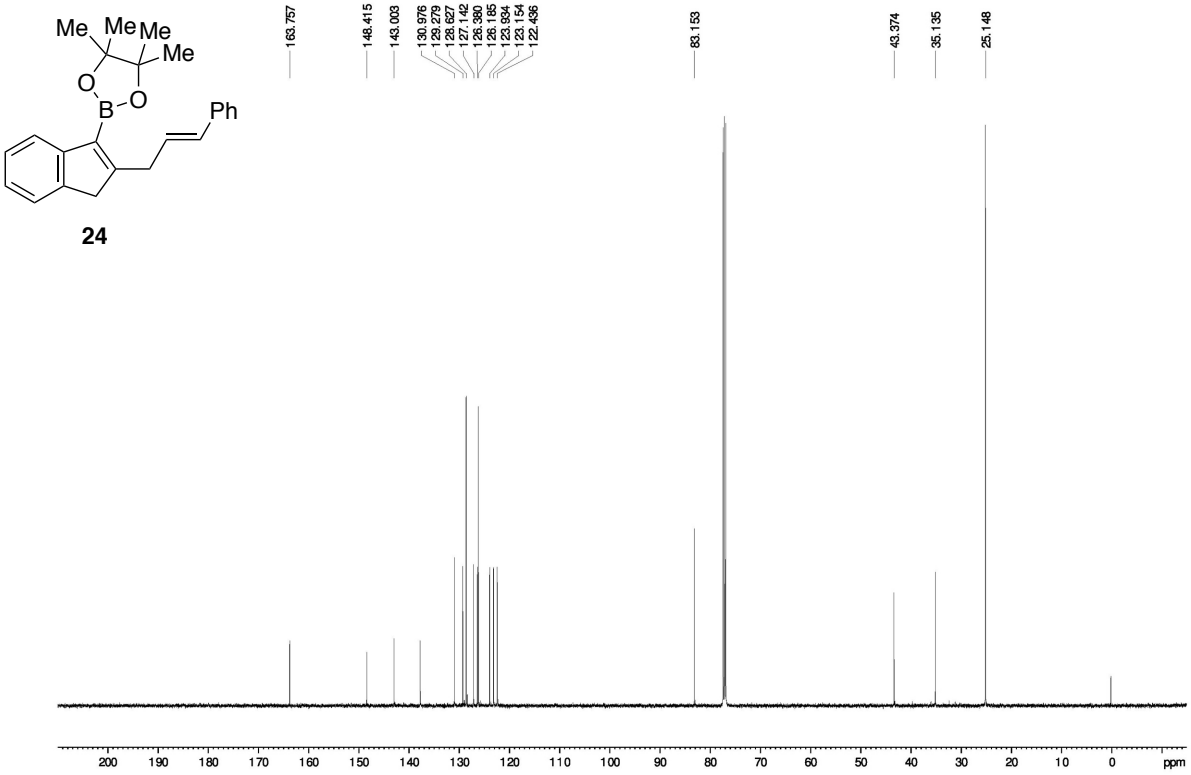
23l,^{13}C NMR (126 MHz, $CDCl_3$) ^{19}F NMR



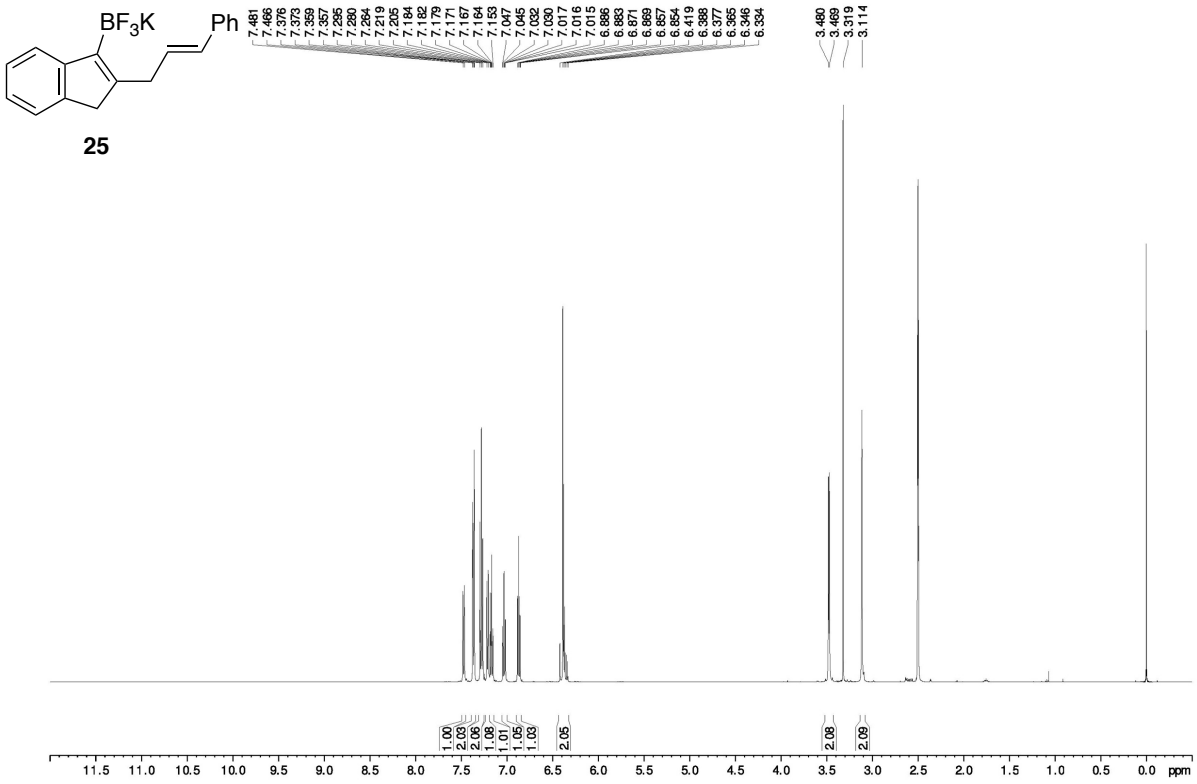
24, ^{1}H NMR (500 MHz, $CDCl_3$)



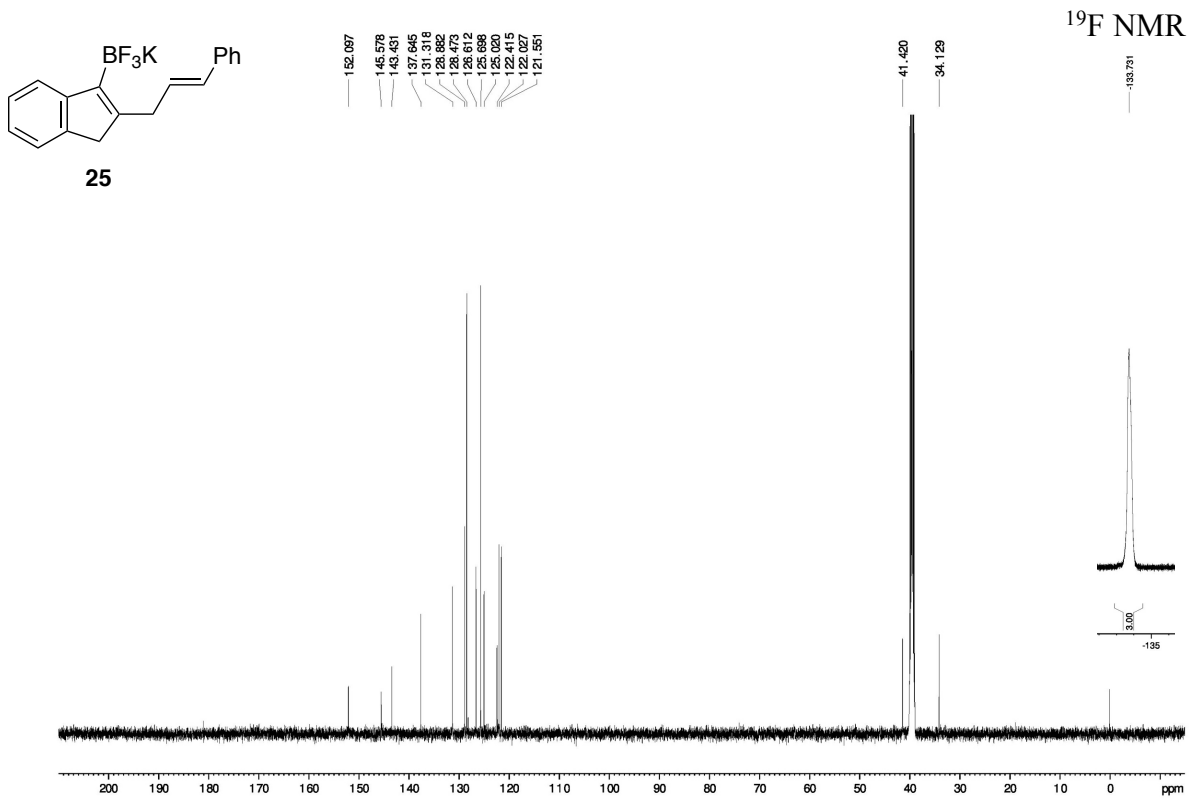
24,^{13}C NMR (126 MHz, $CDCl_3$)



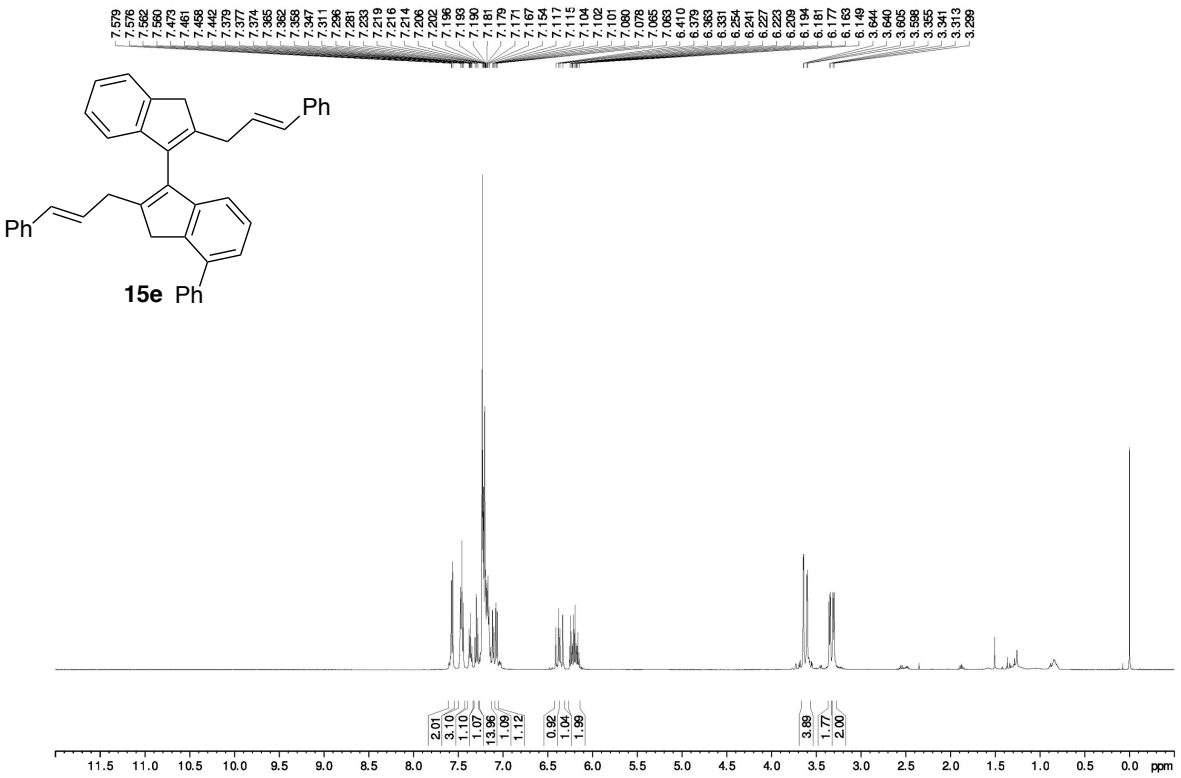
25, ^{1}H NMR (500 MHz, $CDCl_3$)



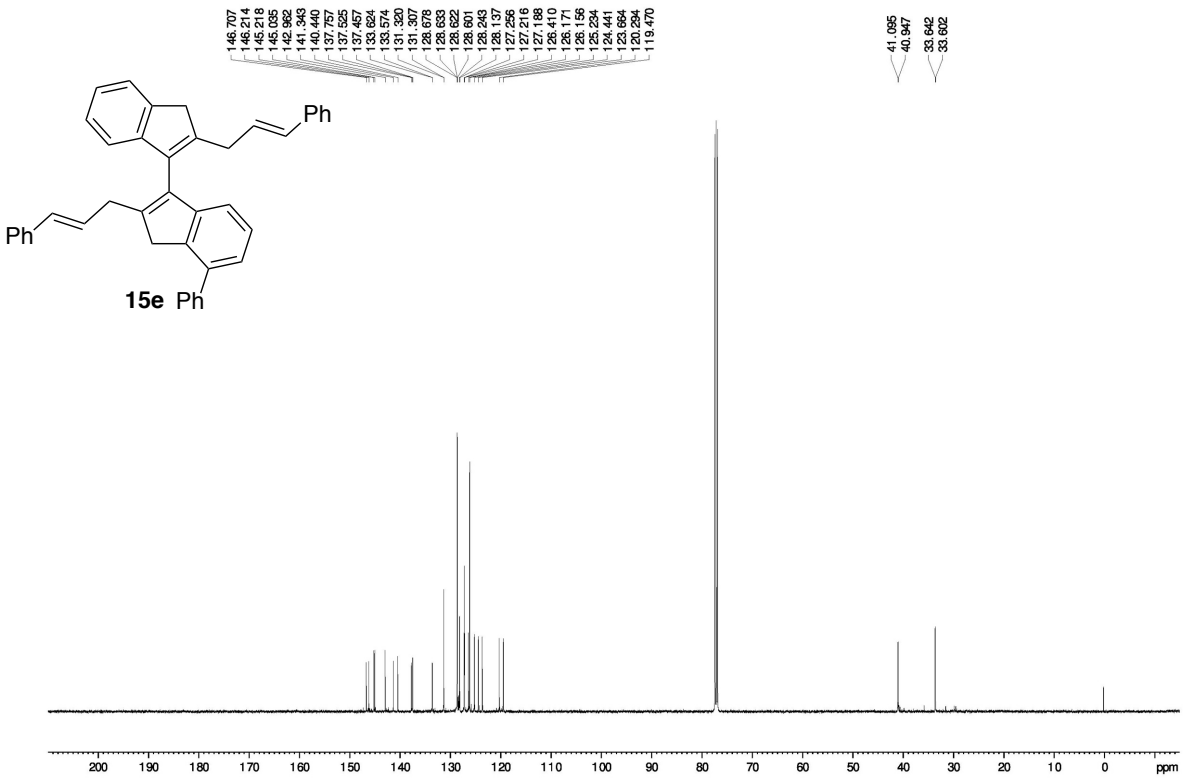
25,^{13}C NMR (126 MHz, $CDCl_3$)



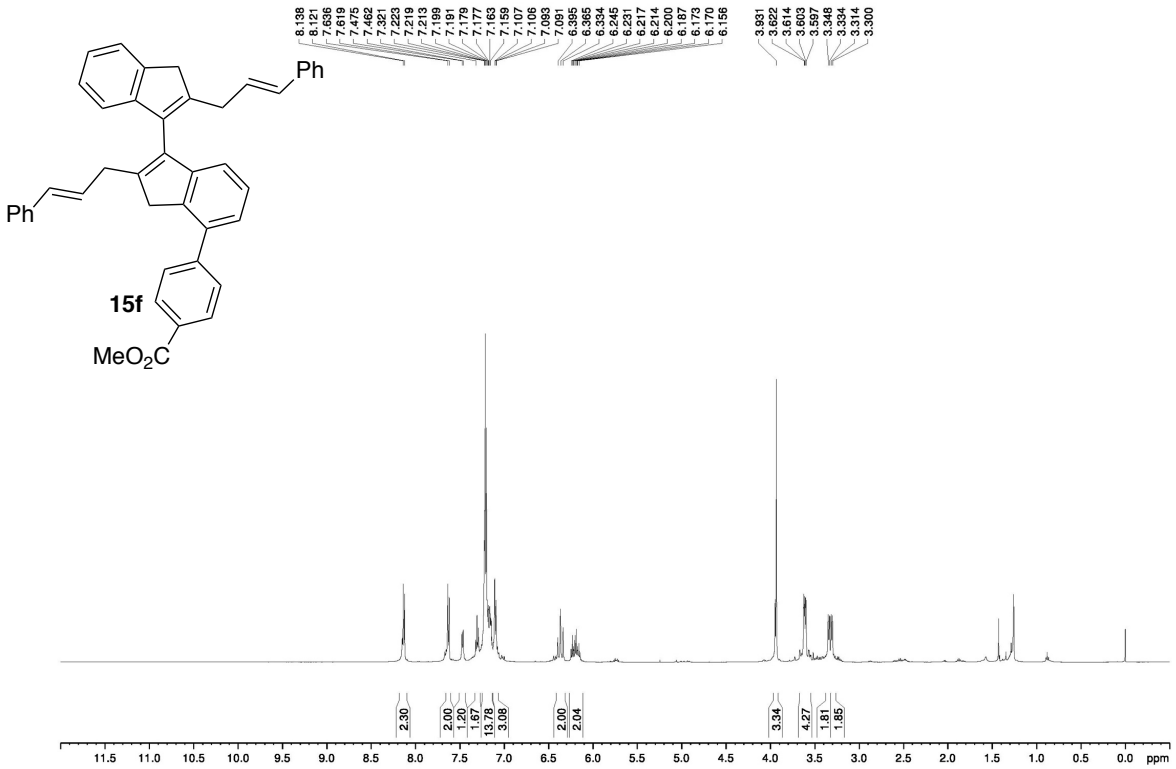
15e, ^{1}H NMR (500 MHz, $CDCl_3$)



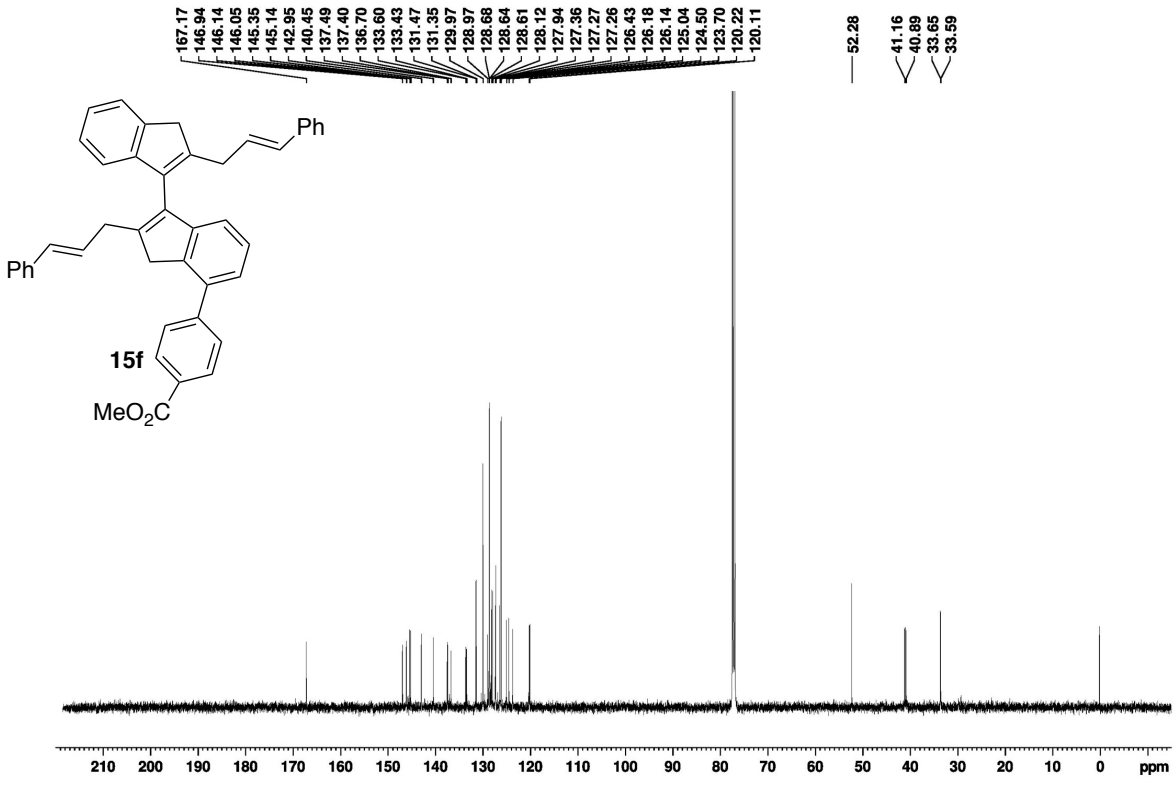
15e, ^{13}C NMR (126 MHz, $CDCl_3$)



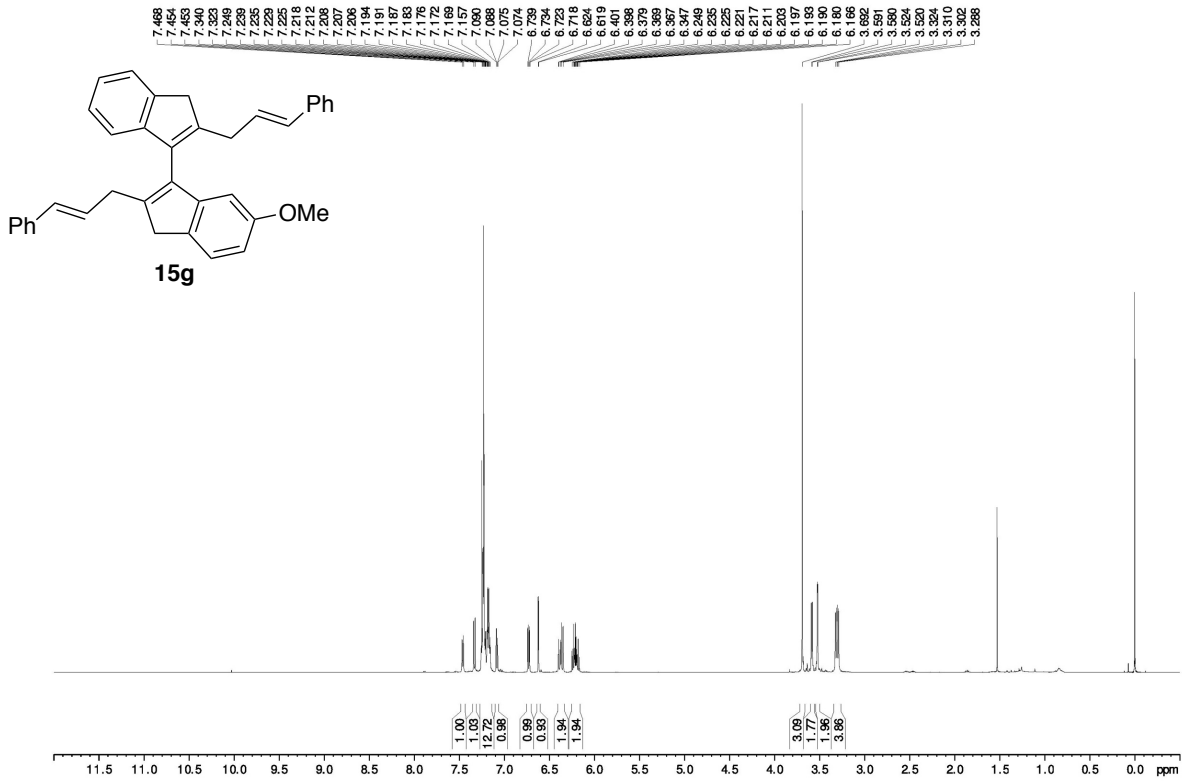
15f, ^{1}H NMR (500 MHz, $CDCl_3$)



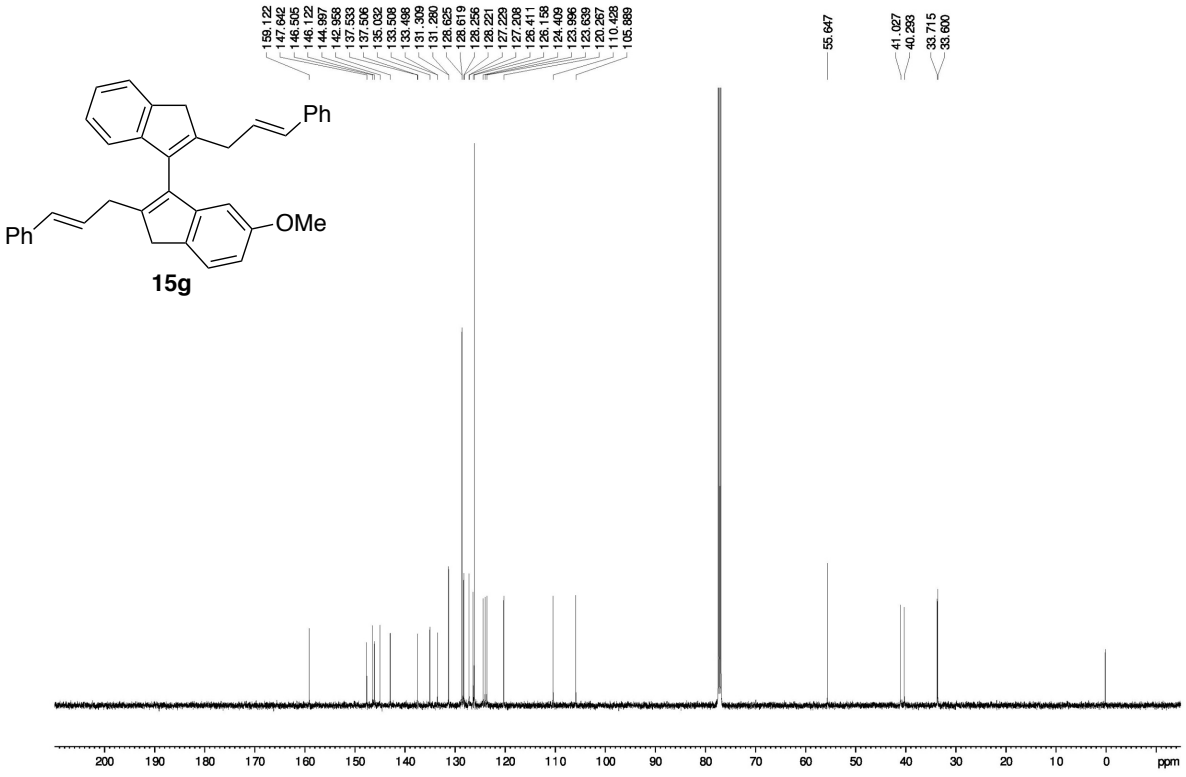
15f, ^{13}C NMR (126 MHz, $CDCl_3$)



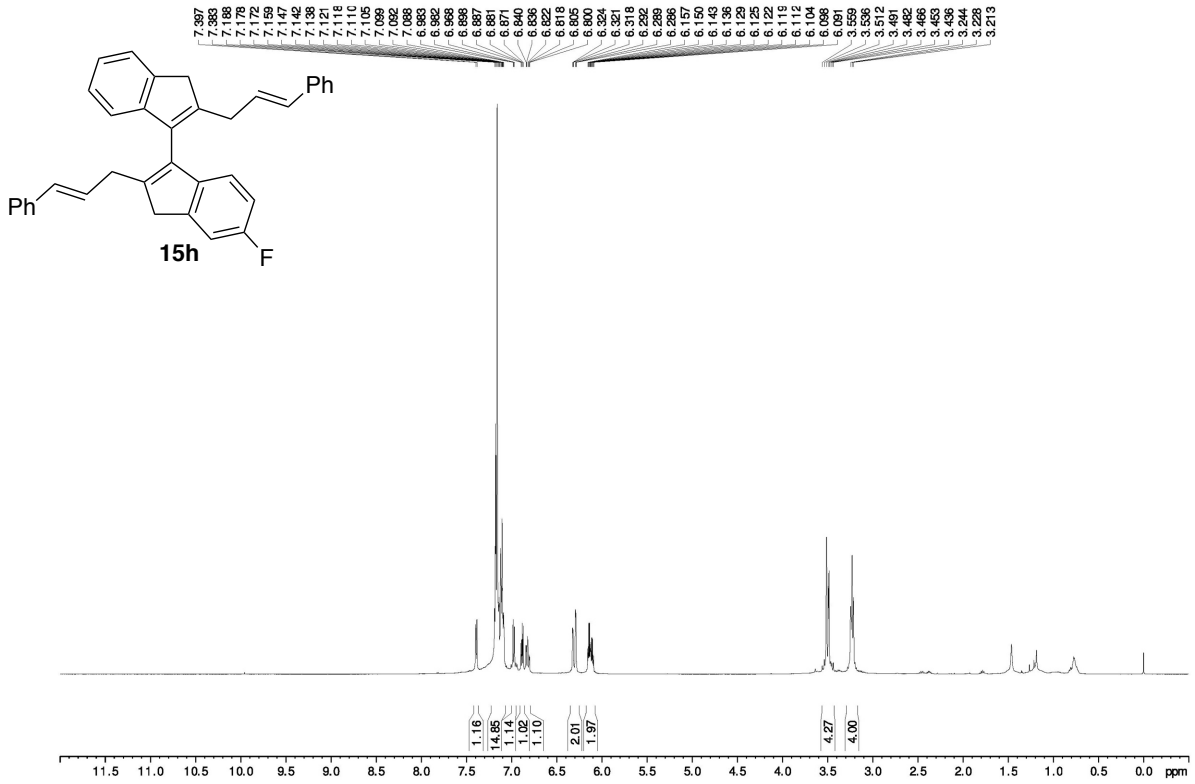
15g, ^{1}H NMR (500 MHz, $CDCl_3$)



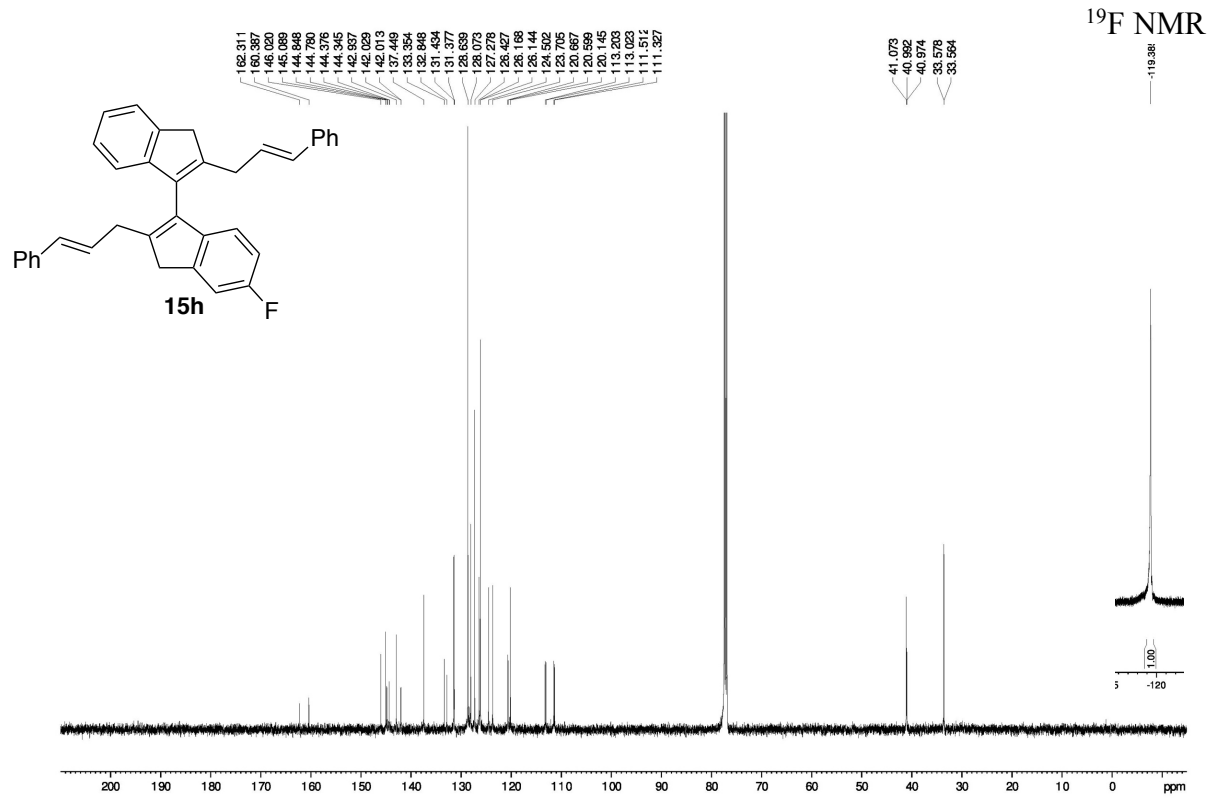
15g, ^{13}C NMR (126 MHz, $CDCl_3$)



15h, ^{1}H NMR (500 MHz, $CDCl_3$)

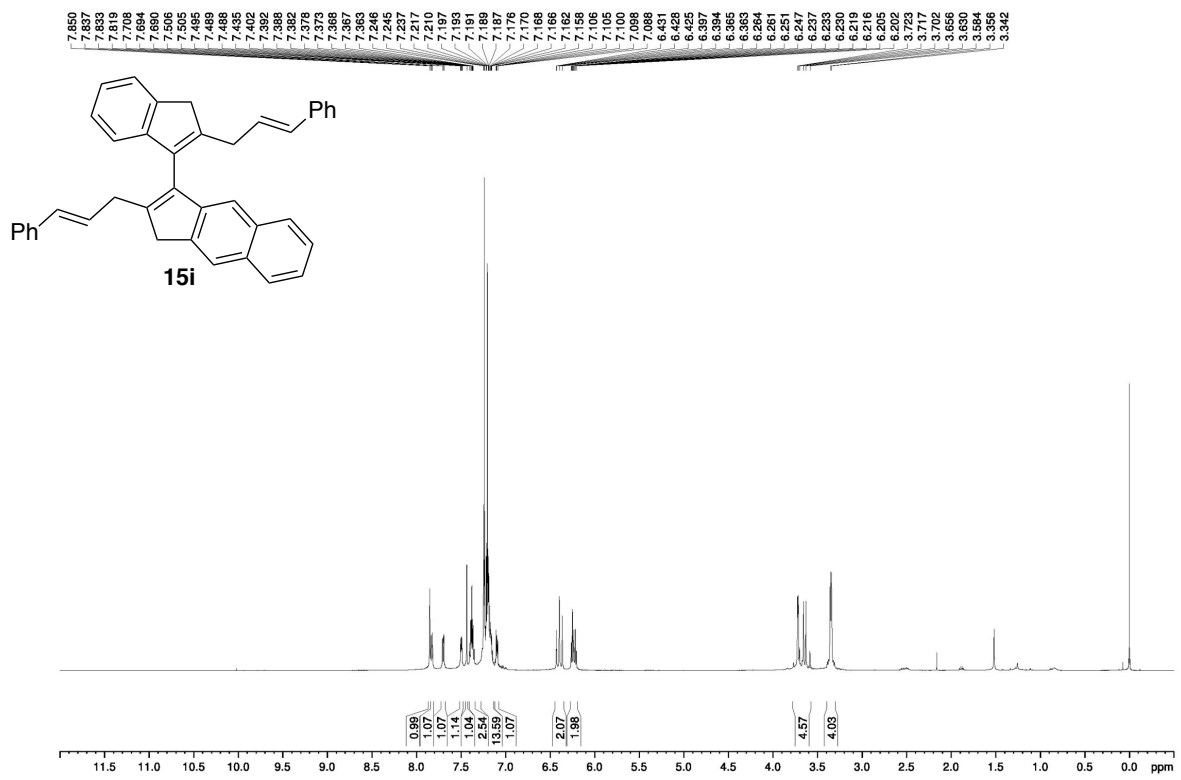


15h, ^{13}C NMR (126 MHz, $CDCl_3$)

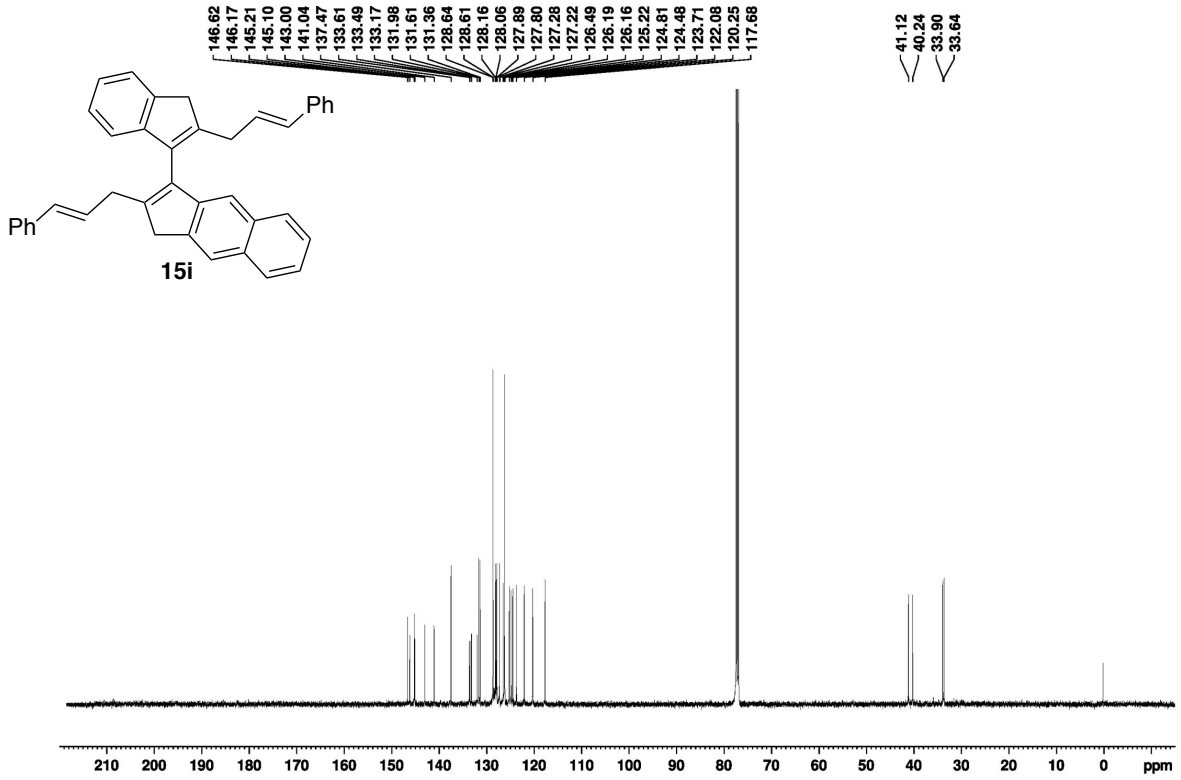


^{19}F NMR

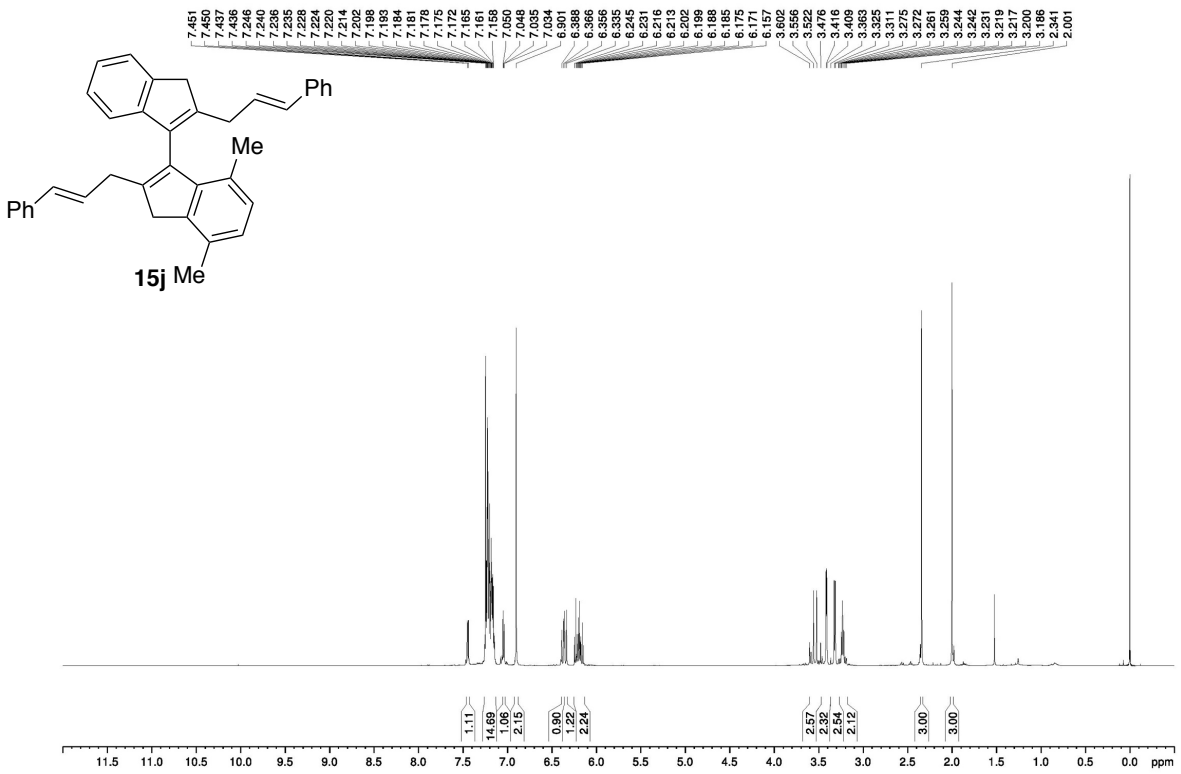
15i, ^{1}H NMR (500 MHz, $CDCl_3$)



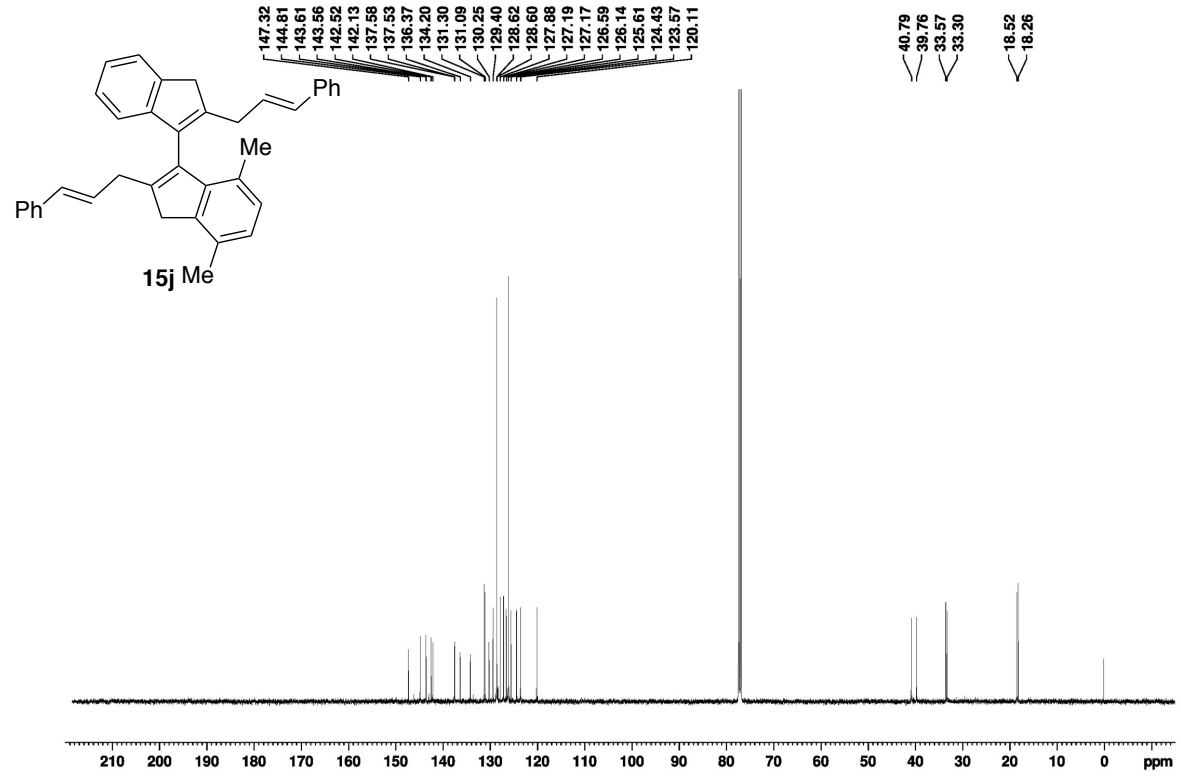
15i, ^{13}C NMR (126 MHz, $CDCl_3$)



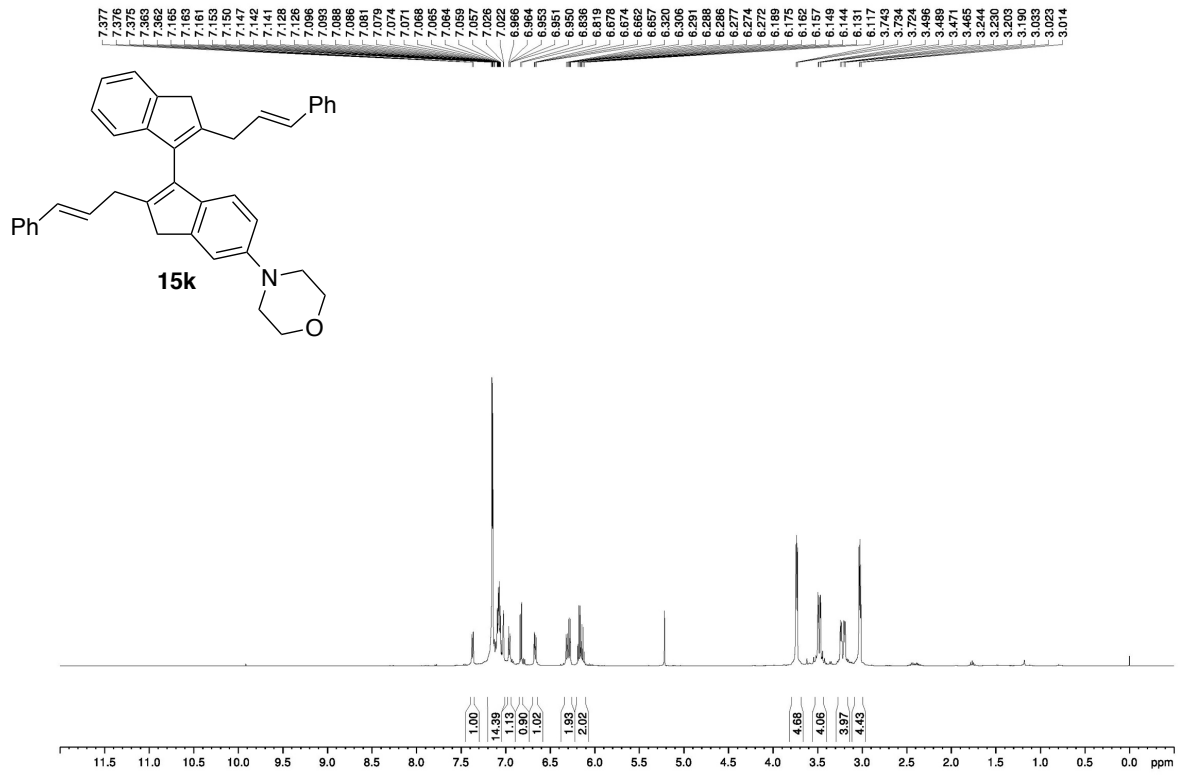
15j, ^{1}H NMR (500 MHz, $CDCl_3$)



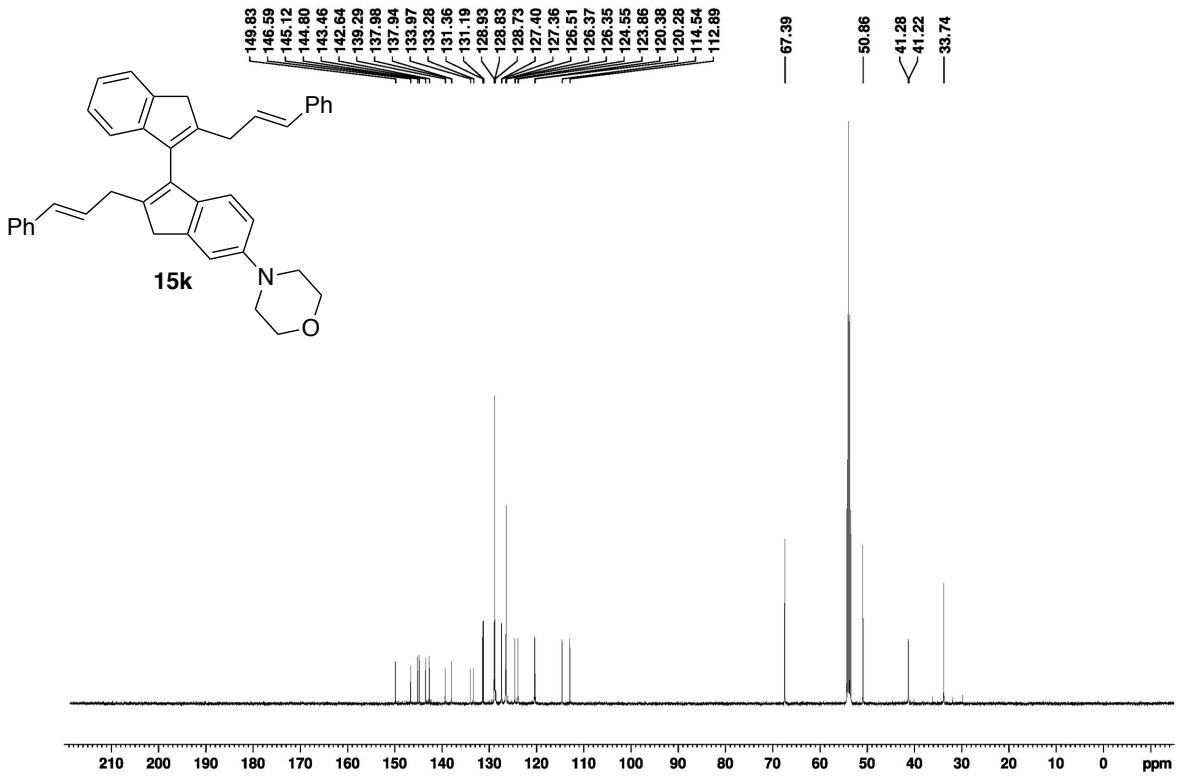
15j, ^{13}C NMR (126 MHz, $CDCl_3$)



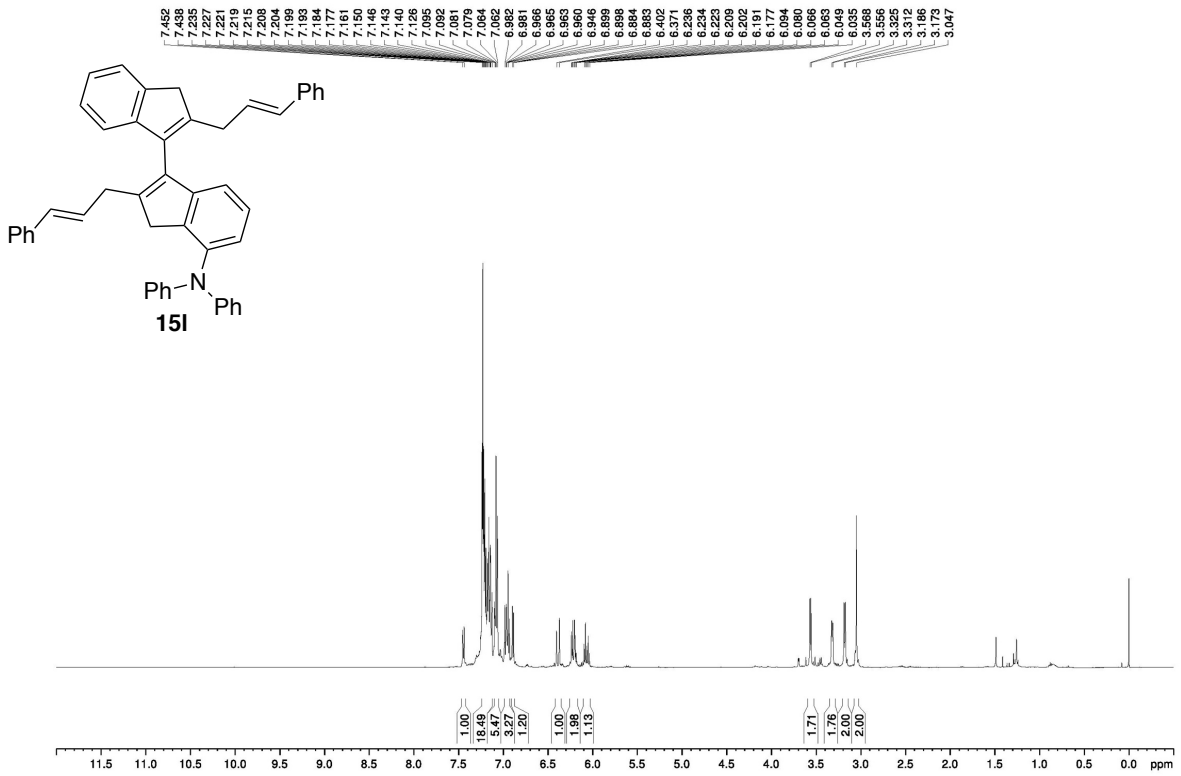
15k, ^{1}H NMR (500 MHz, CD_2Cl_2)



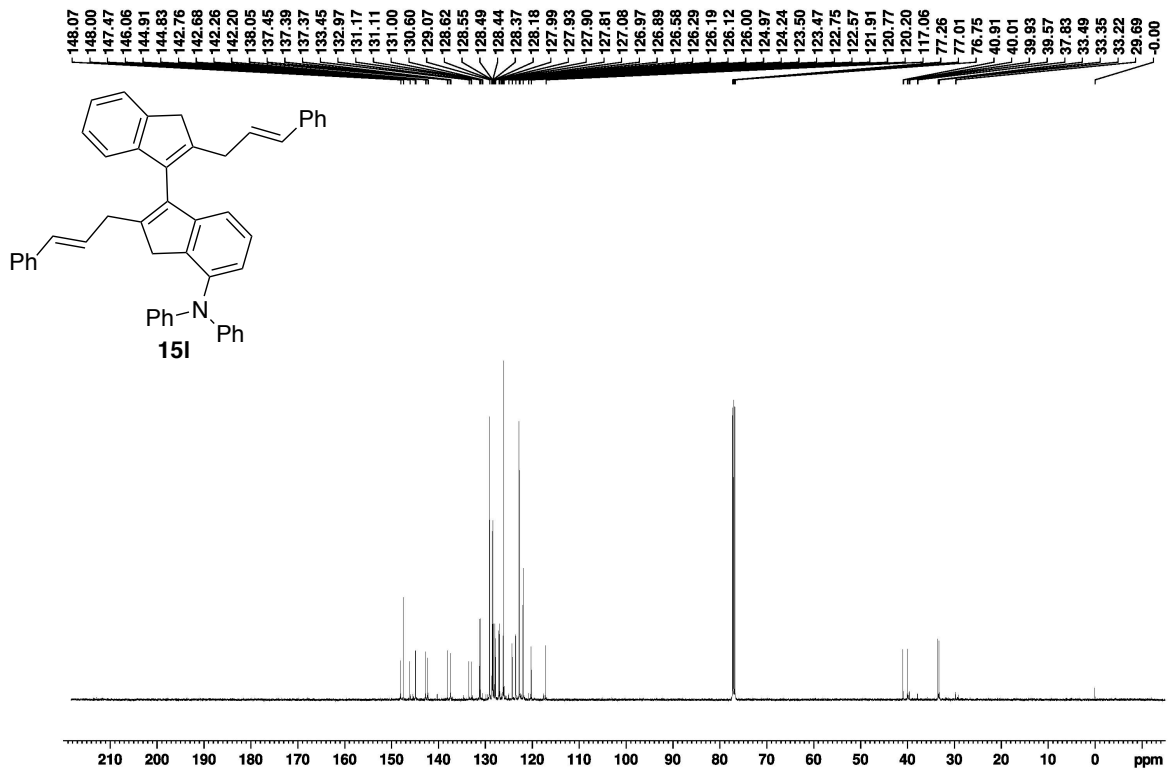
15k, ^{13}C NMR (126 MHz, $CDCl_3$)



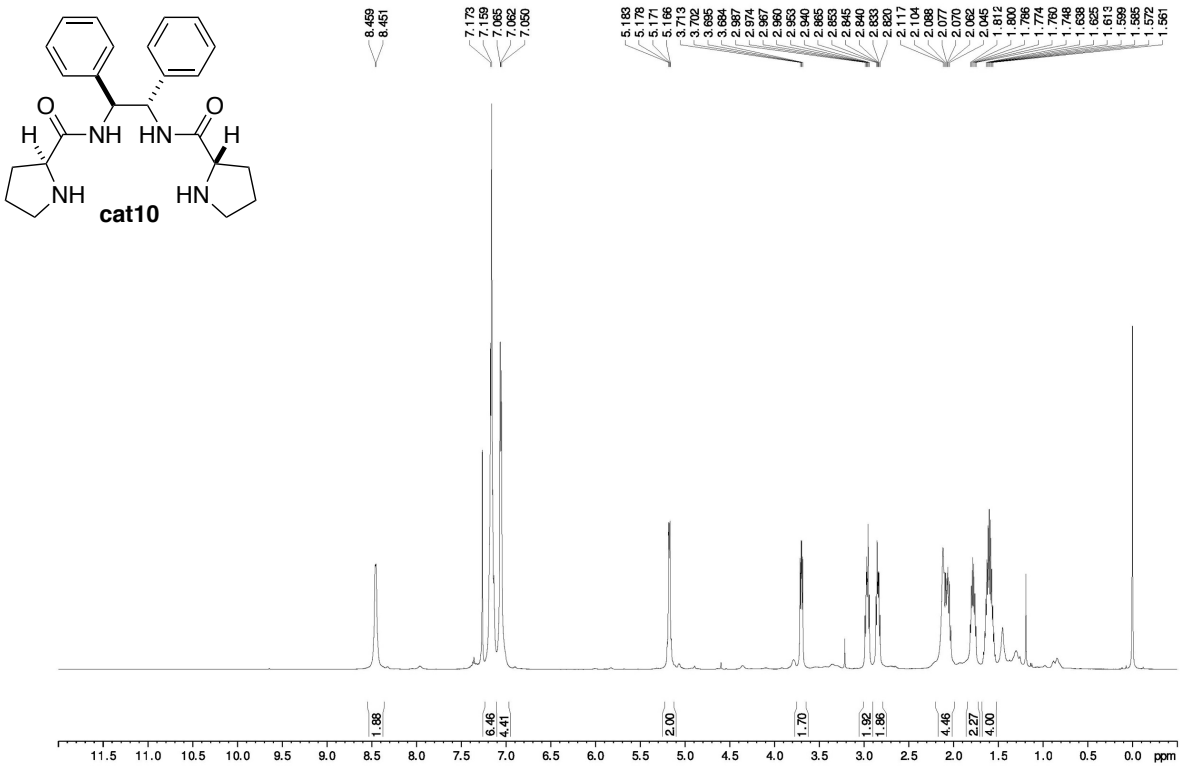
15l, ^{1}H NMR (500 MHz, $CDCl_3$)



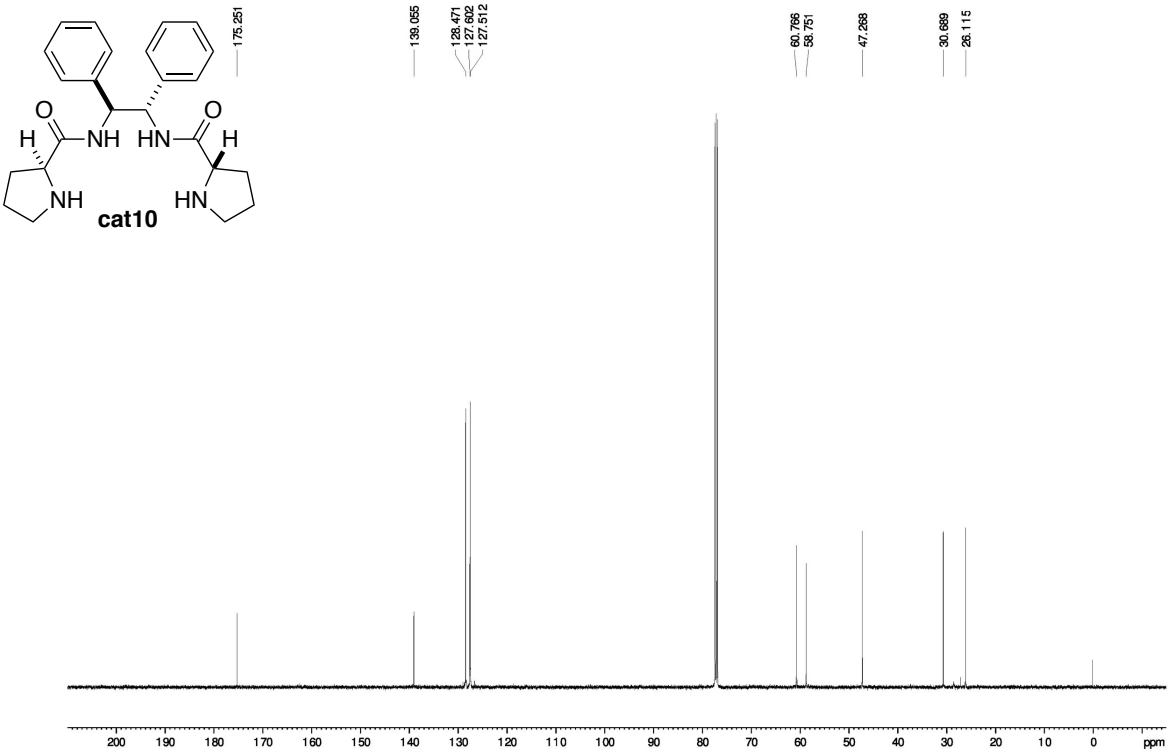
15l, ^{13}C NMR (126 MHz, $CDCl_3$)



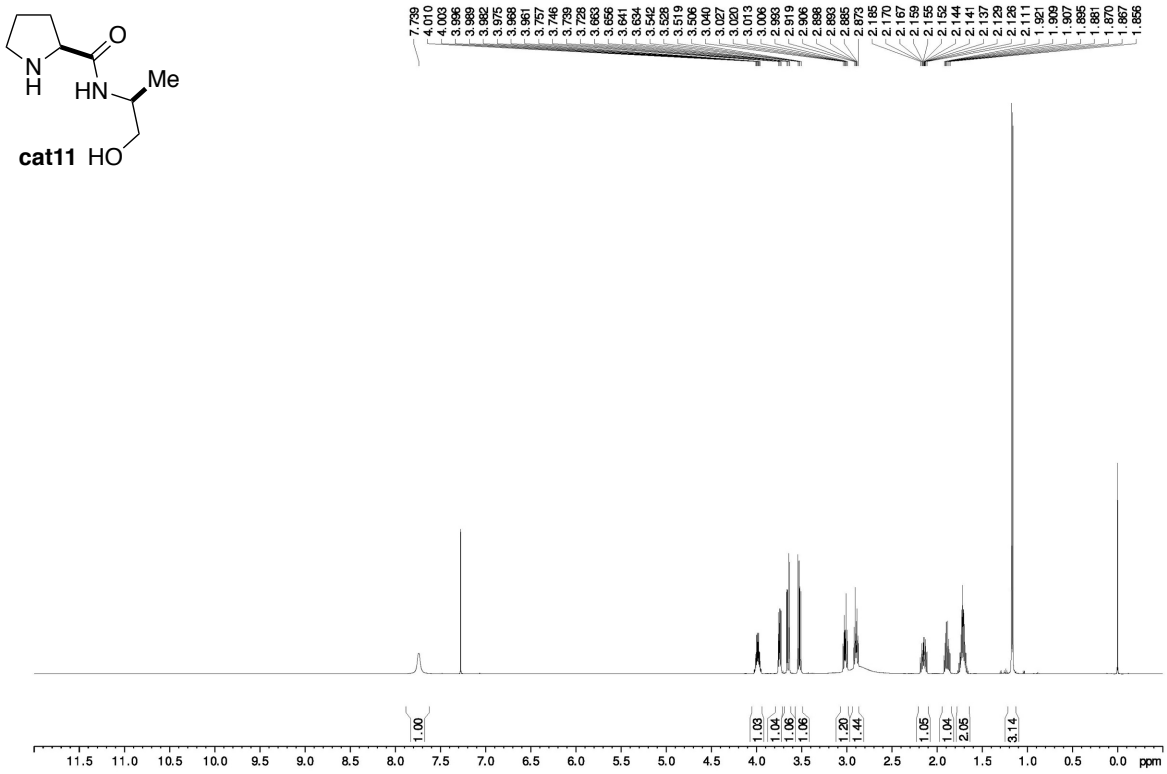
cat10, ^{1}H NMR (500 MHz, $CDCl_3$)



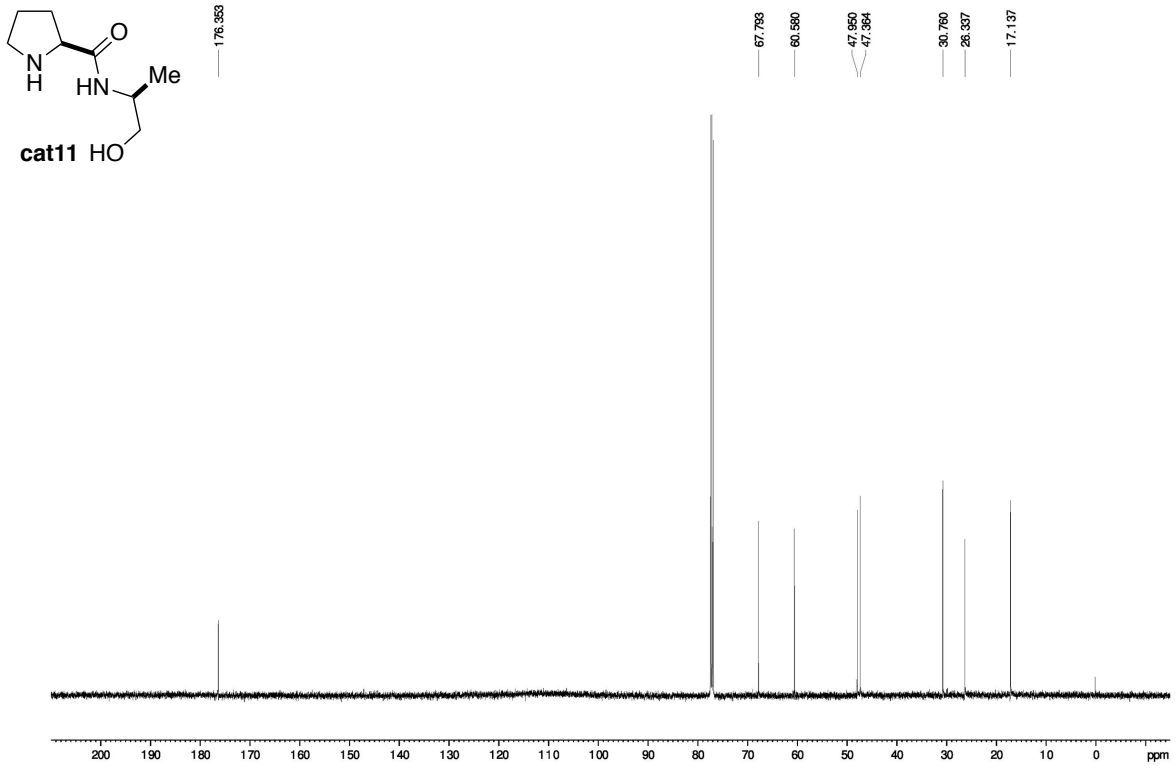
cat10, ^{13}C NMR (126 MHz, $CDCl_3$)



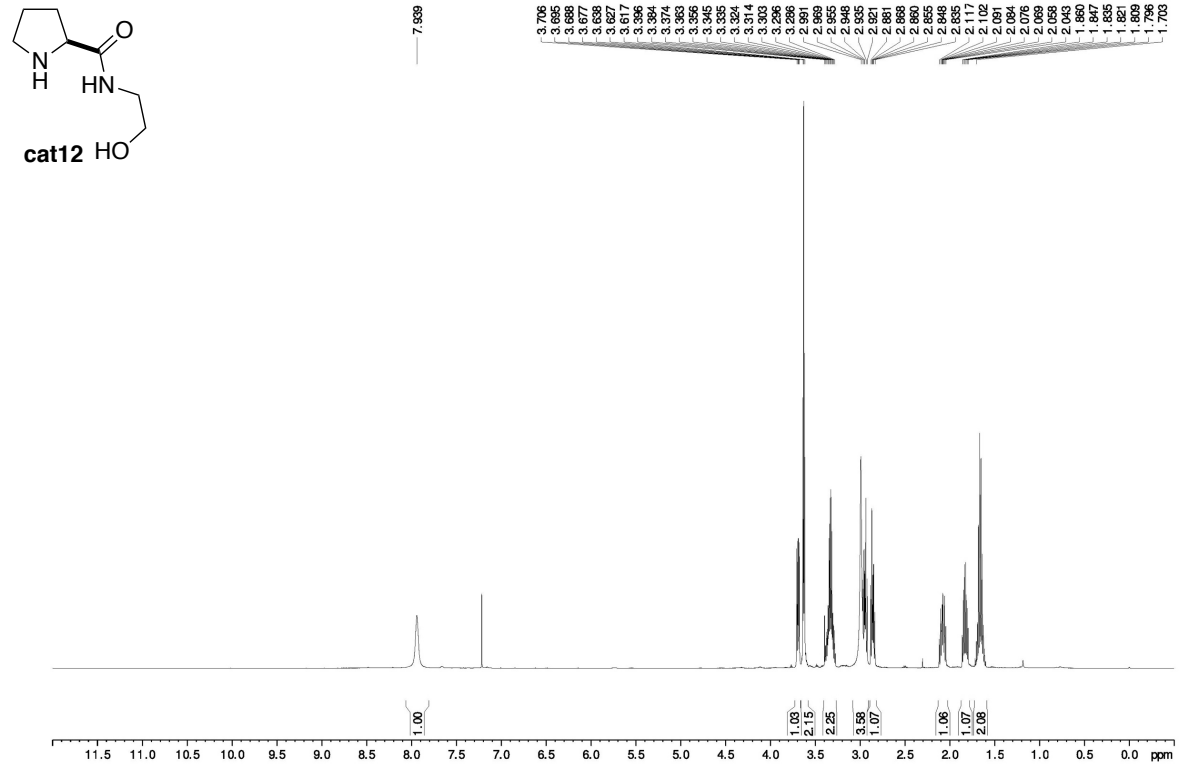
cat11, ^{1}H NMR (500 MHz, $CDCl_3$)



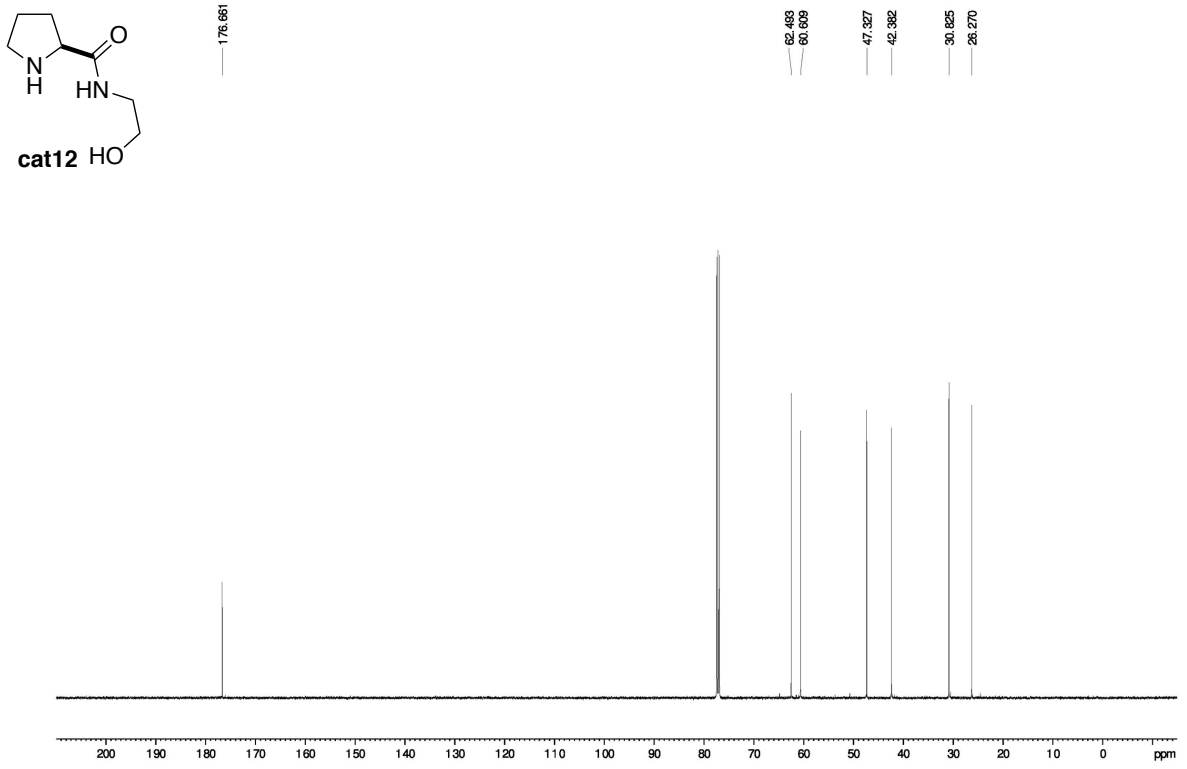
cat11, ^{13}C NMR (126 MHz, $CDCl_3$)



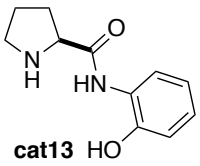
cat12, ^{1}H NMR (500 MHz, $CDCl_3$)

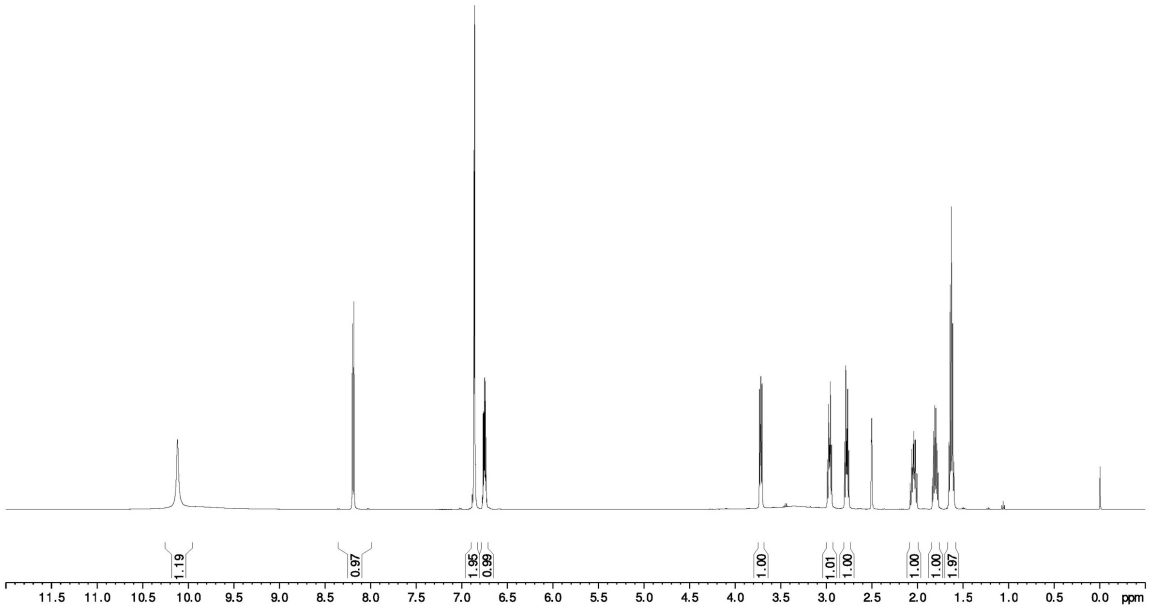


cat12, ^{13}C NMR (126 MHz, $CDCl_3$)

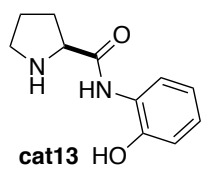


cat13, ^{1}H NMR (500 MHz, $CDCl_3$)

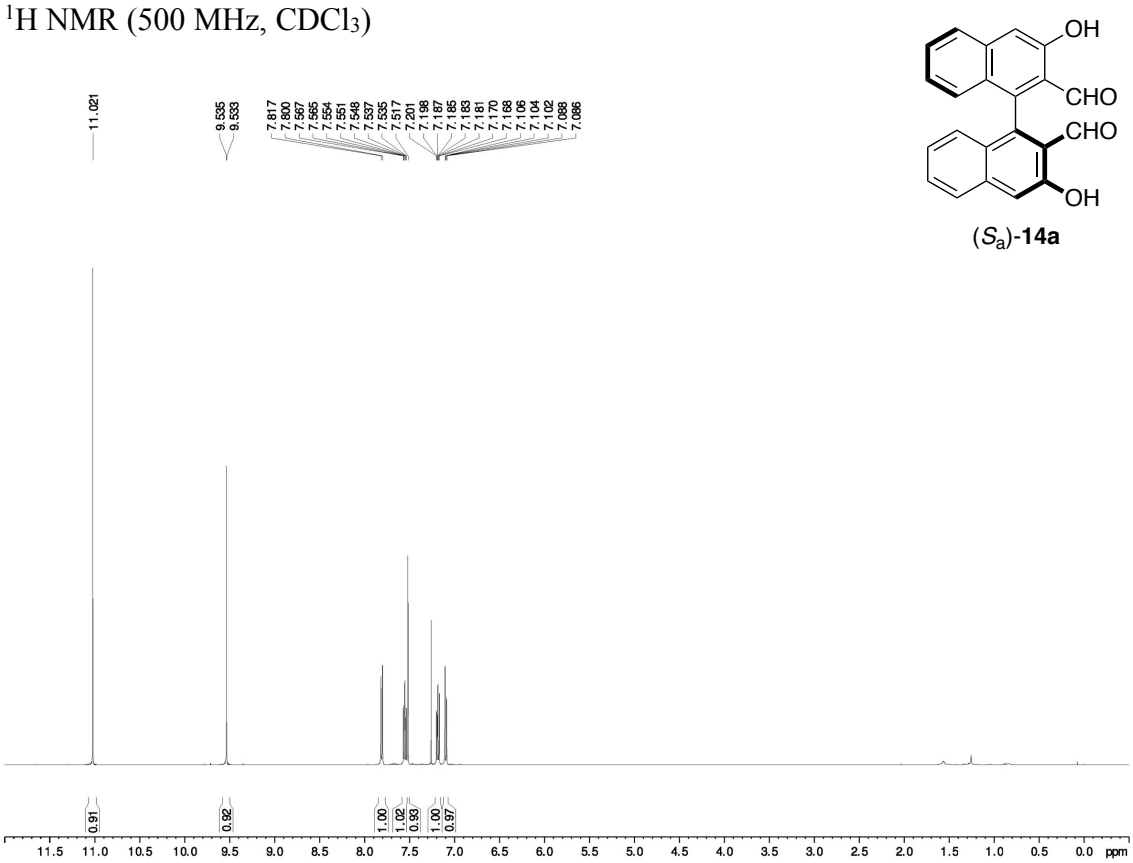




cat13, ^{13}C NMR (126 MHz, $CDCl_3$)

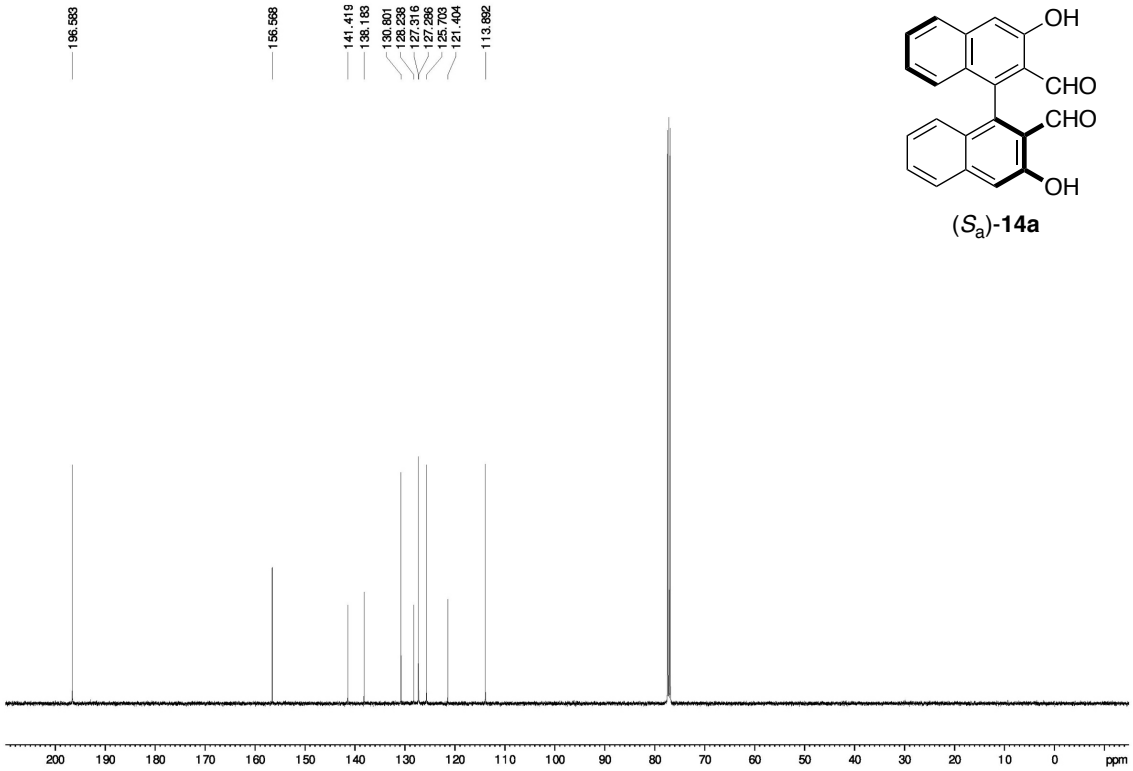


14a, ^{1}H NMR (500 MHz, $CDCl_3$)



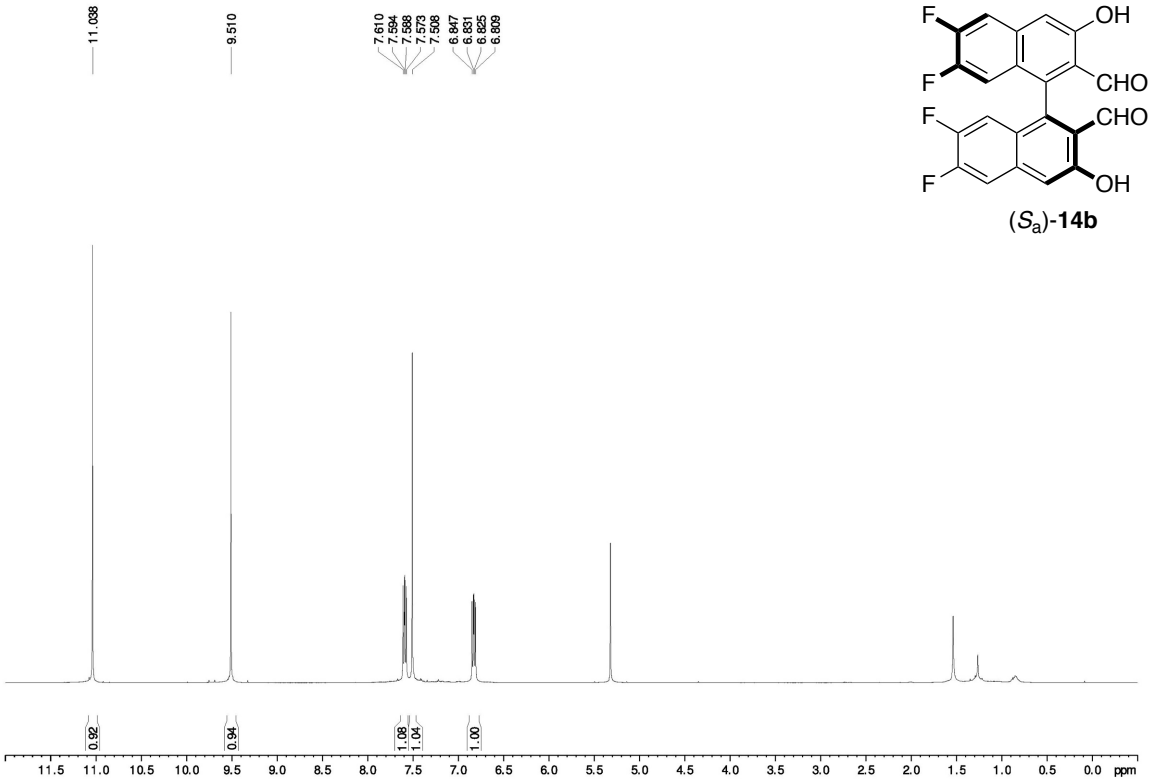
(S_a)-**14a**

14a, ^{13}C NMR (126 MHz, $CDCl_3$)

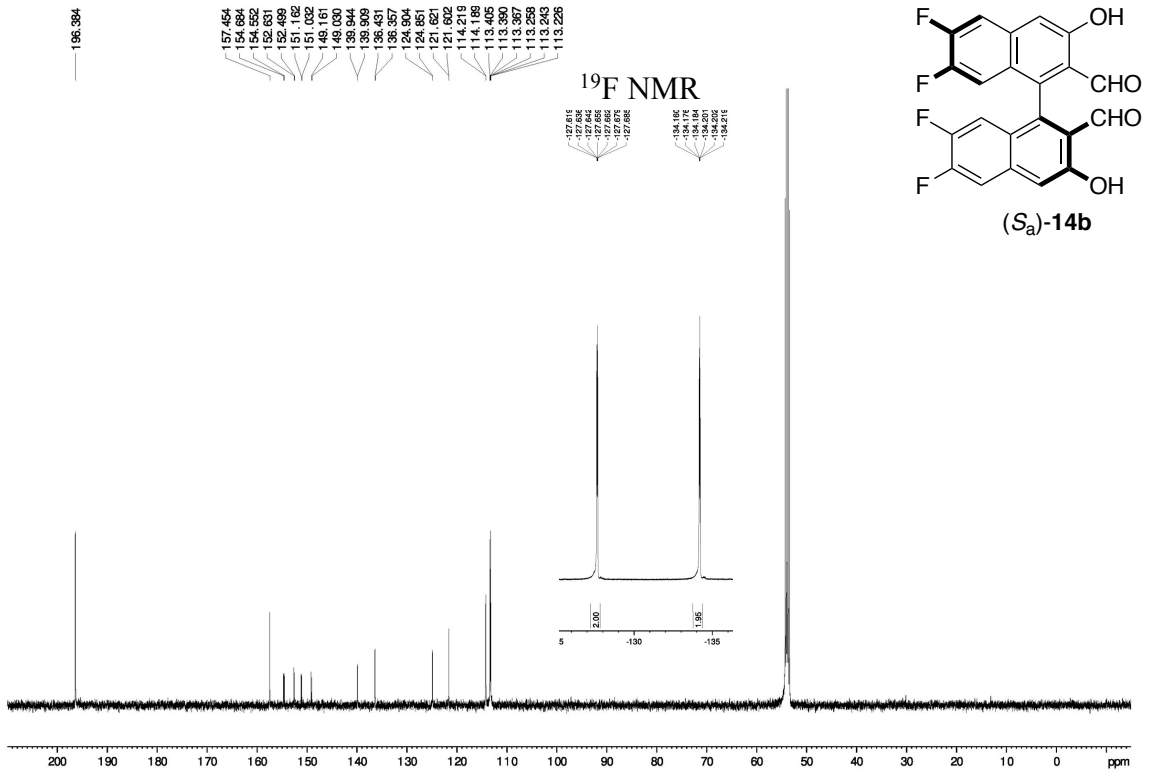


(S_a)-**14a**

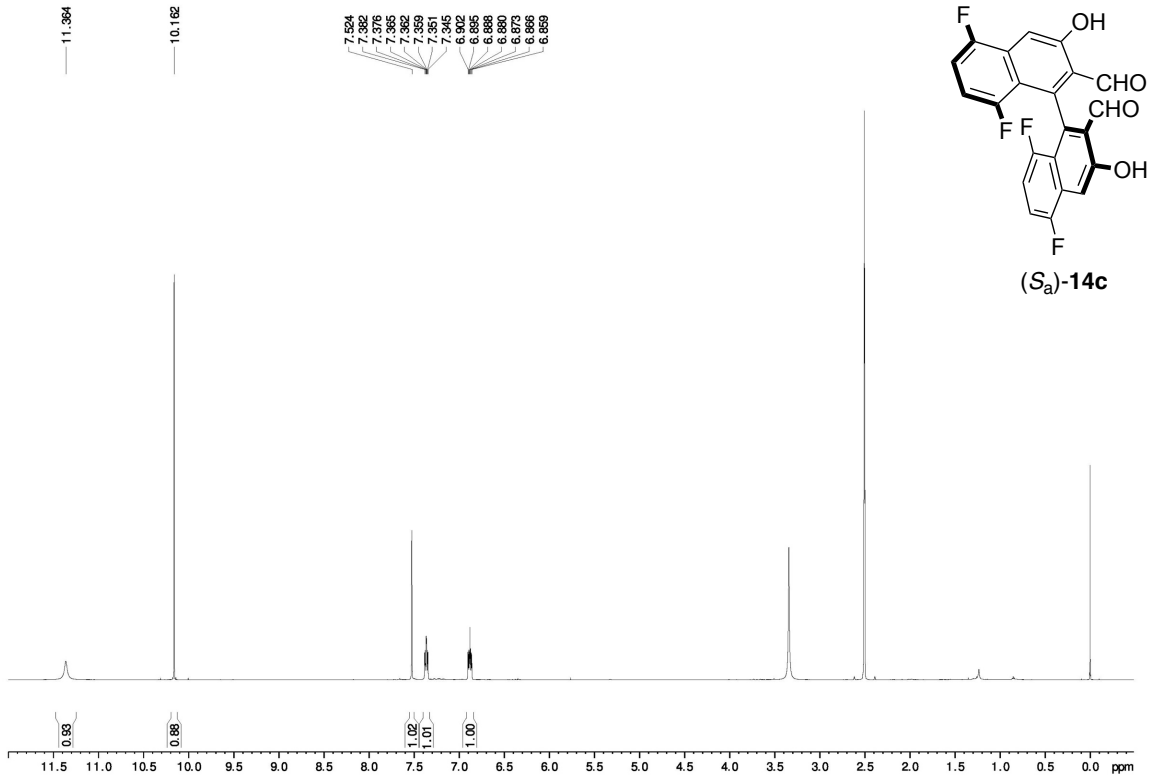
14b, ^{1}H NMR (500 MHz, $CDCl_3$)



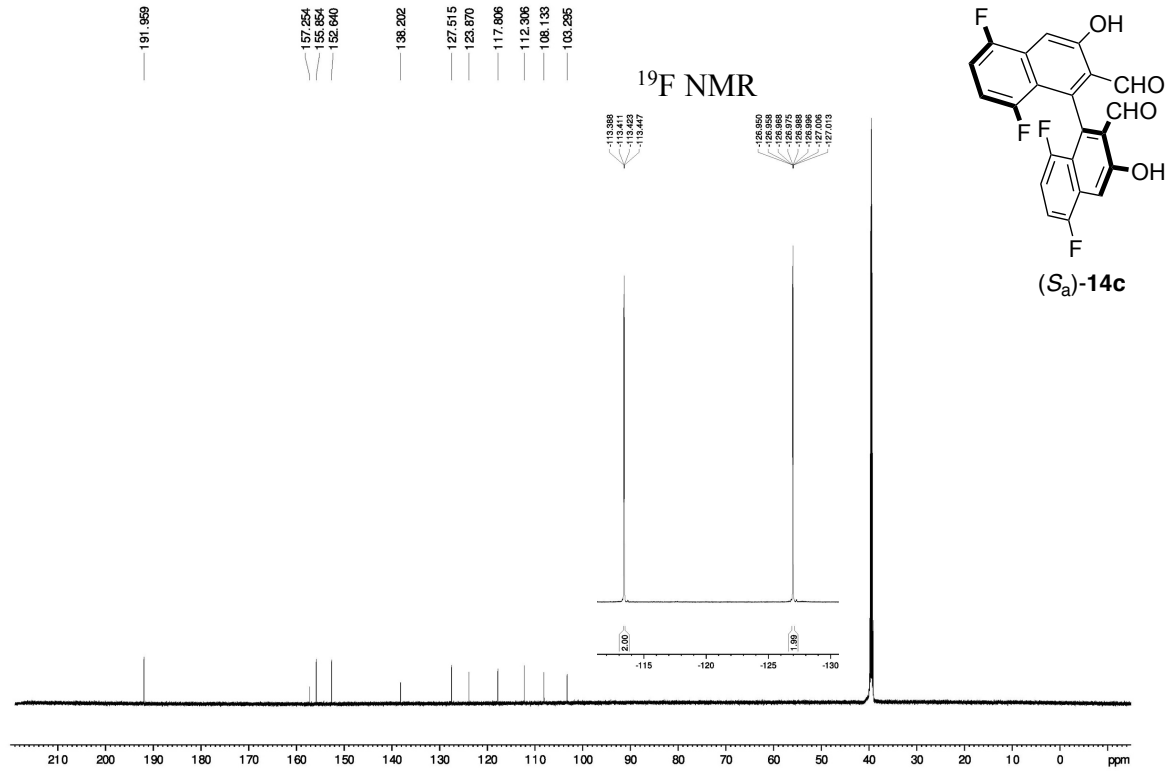
14b, ^{13}C NMR (126 MHz, $CDCl_3$)



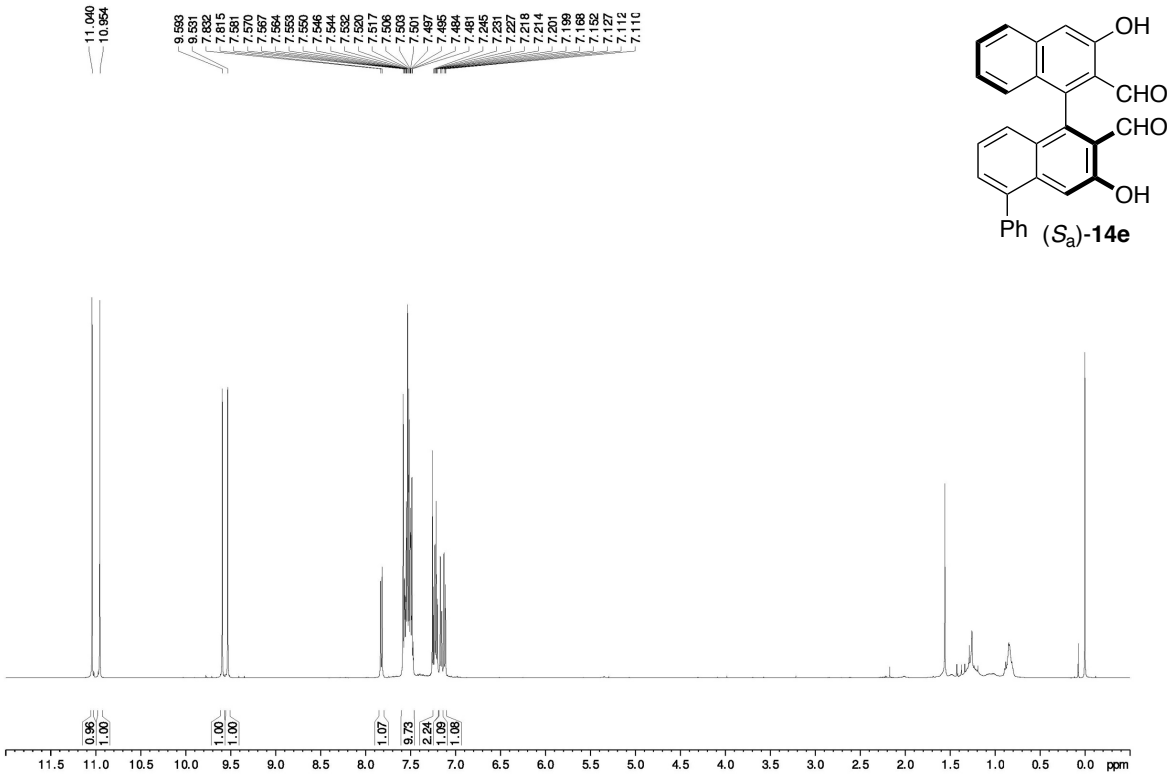
14c, ^{1}H NMR (600 MHz, $(CD_3)_2SO$)



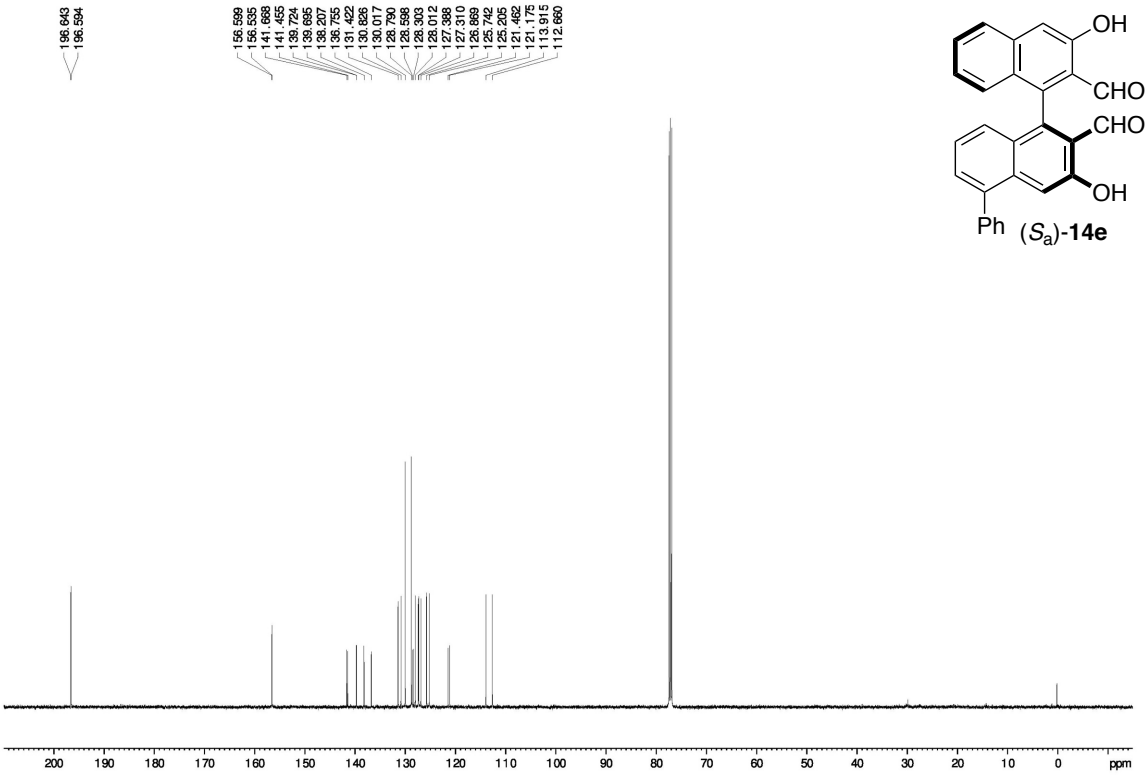
14c, ^{13}C NMR (151 MHz, $(CD_3)_2SO$, ^{1}H cpd (waltz 16), ^{19}F inverse gating (garp 4) decoupling)



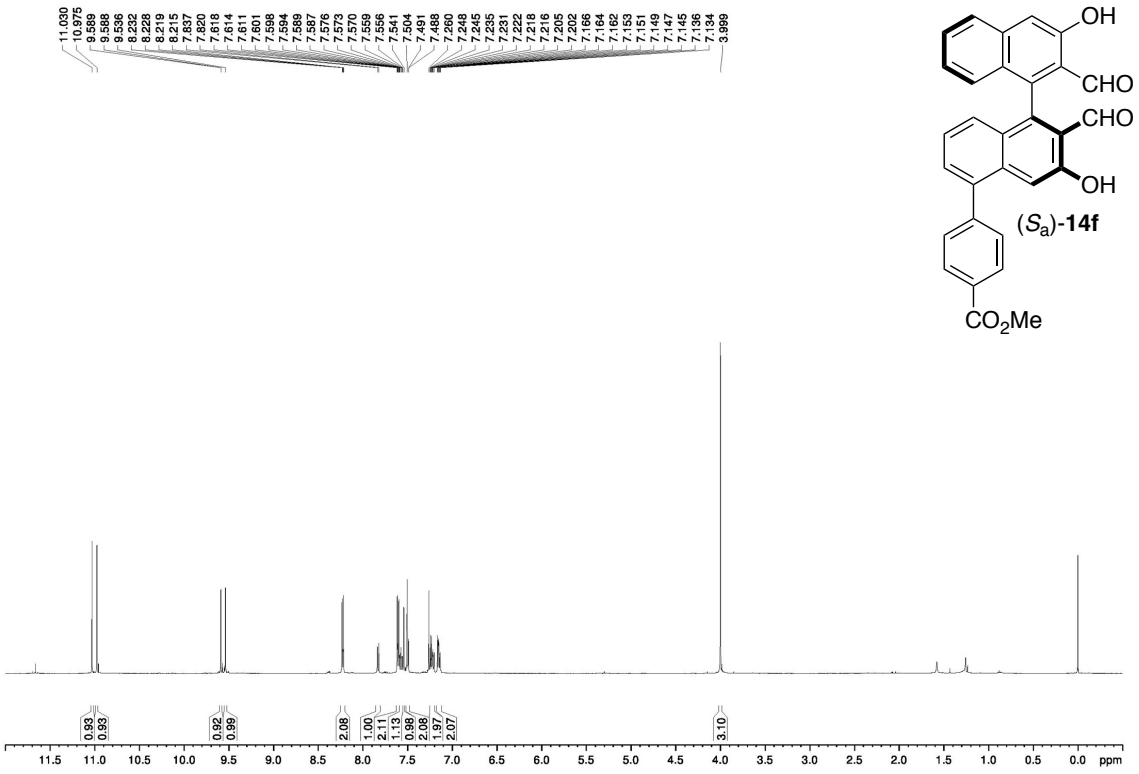
14e, ^{1}H NMR (500 MHz, $CDCl_3$)



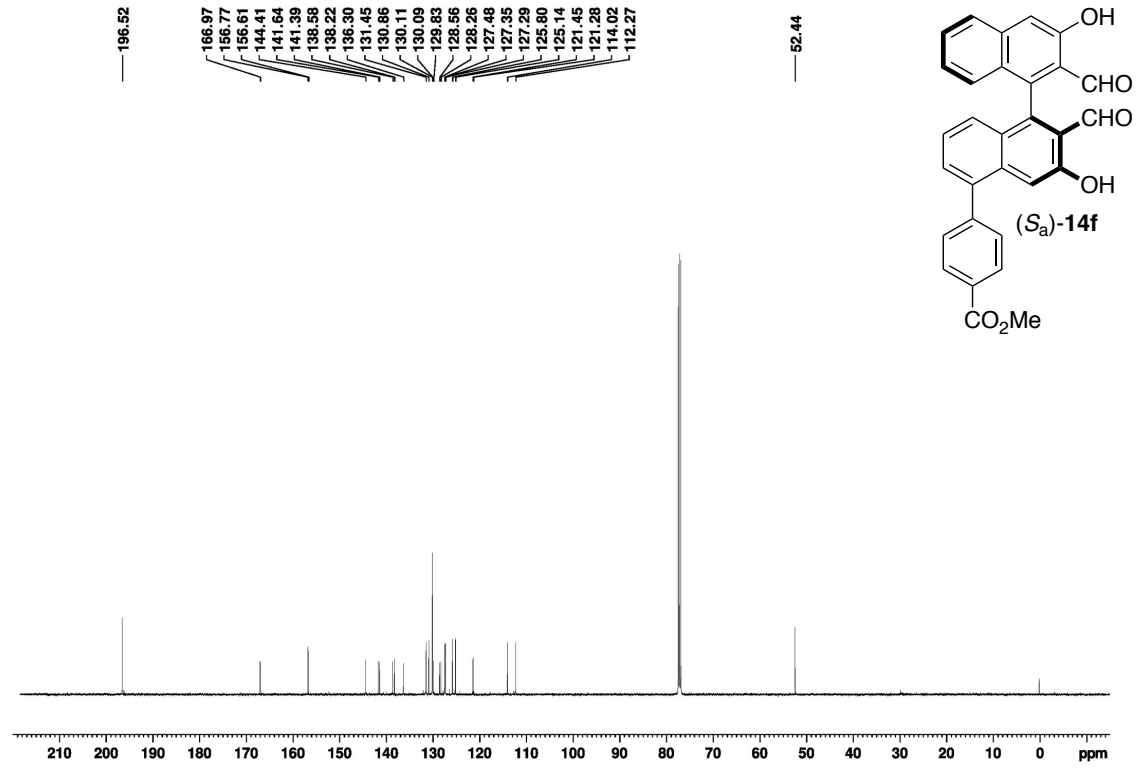
14e, ^{13}C NMR (126 MHz, $CDCl_3$)



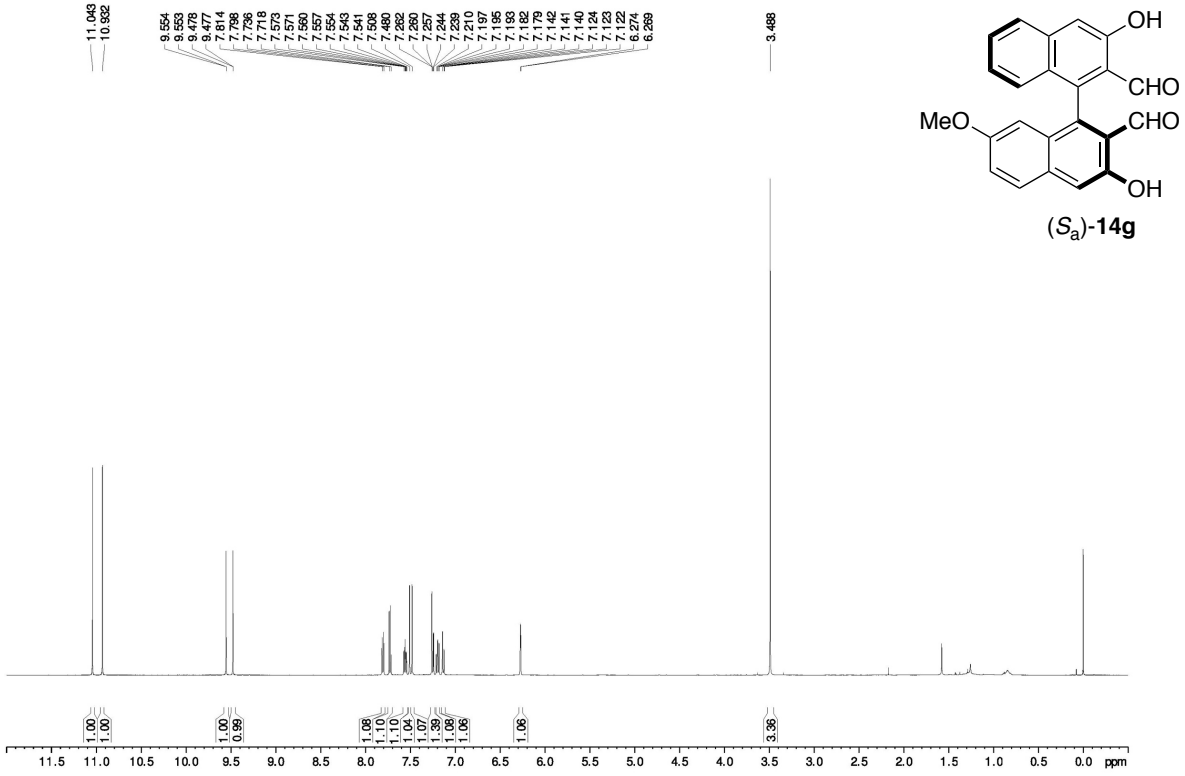
14f, ^{1}H NMR (500 MHz, $CDCl_3$)



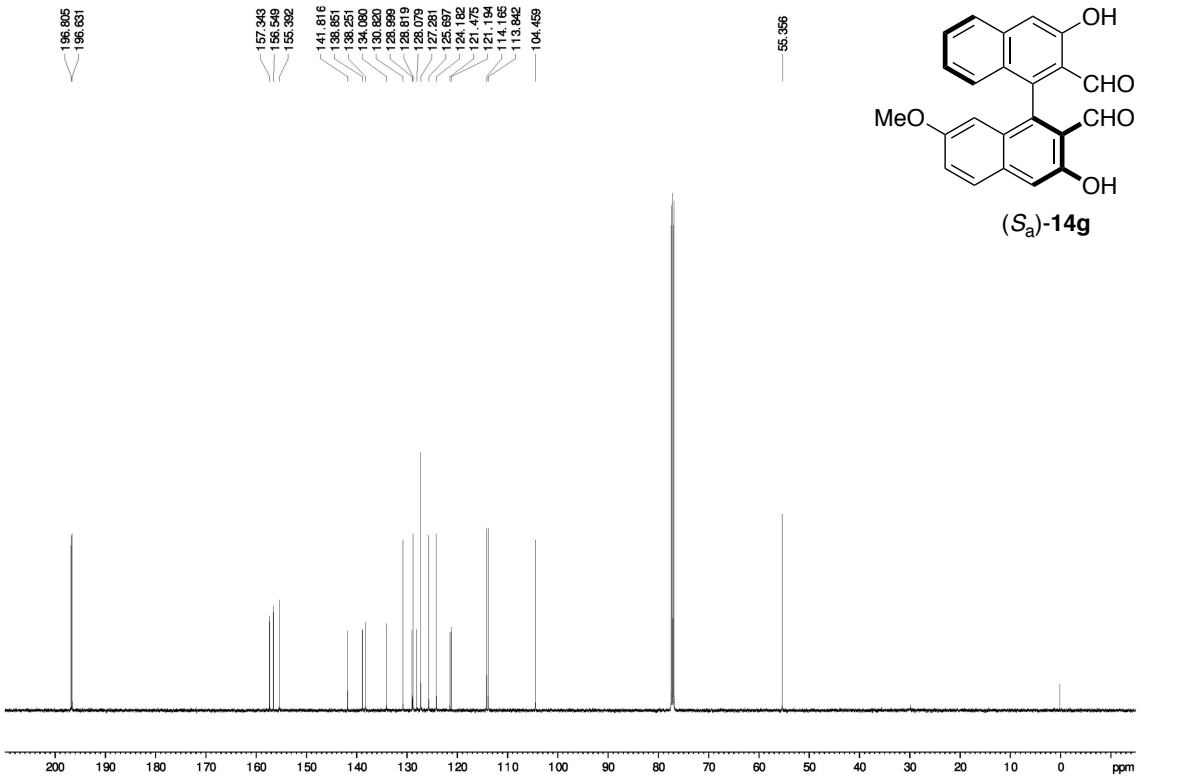
14f, ^{13}C NMR (126 MHz, $CDCl_3$)



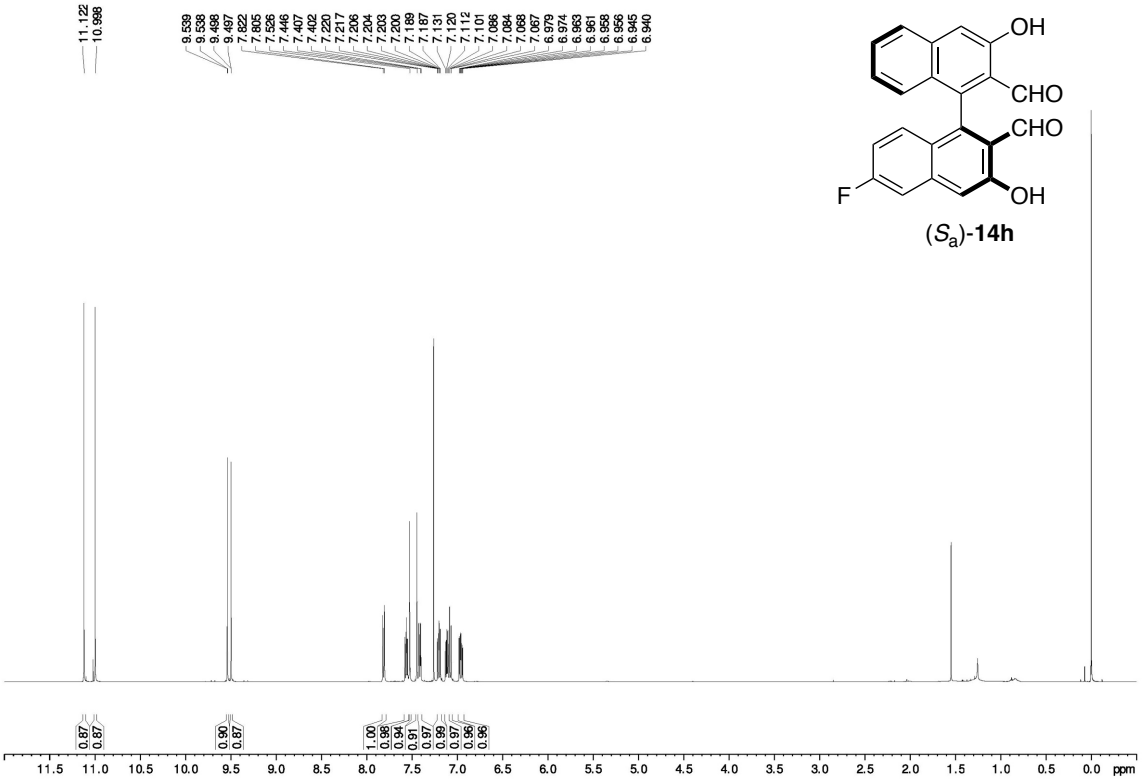
14g, ^{1}H NMR (500 MHz, $CDCl_3$)



14g, ^{13}C NMR (126 MHz, $CDCl_3$)

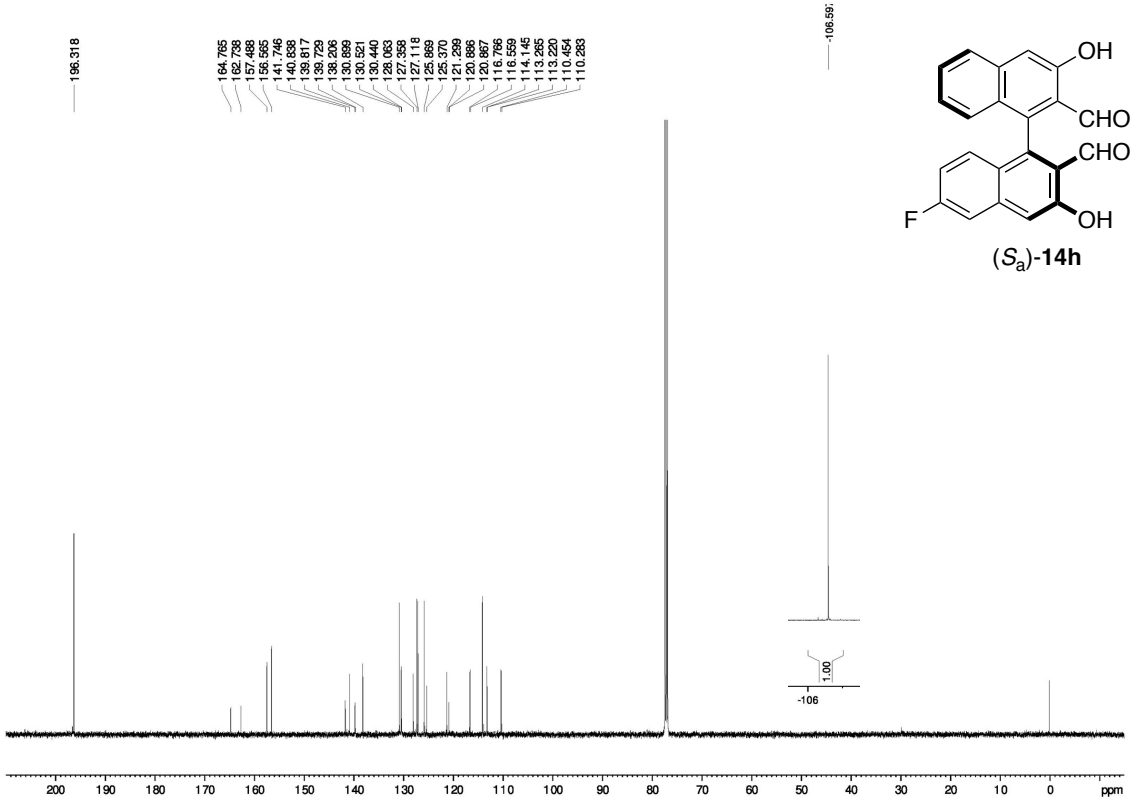


14h, ^{1}H NMR (500 MHz, $CDCl_3$)

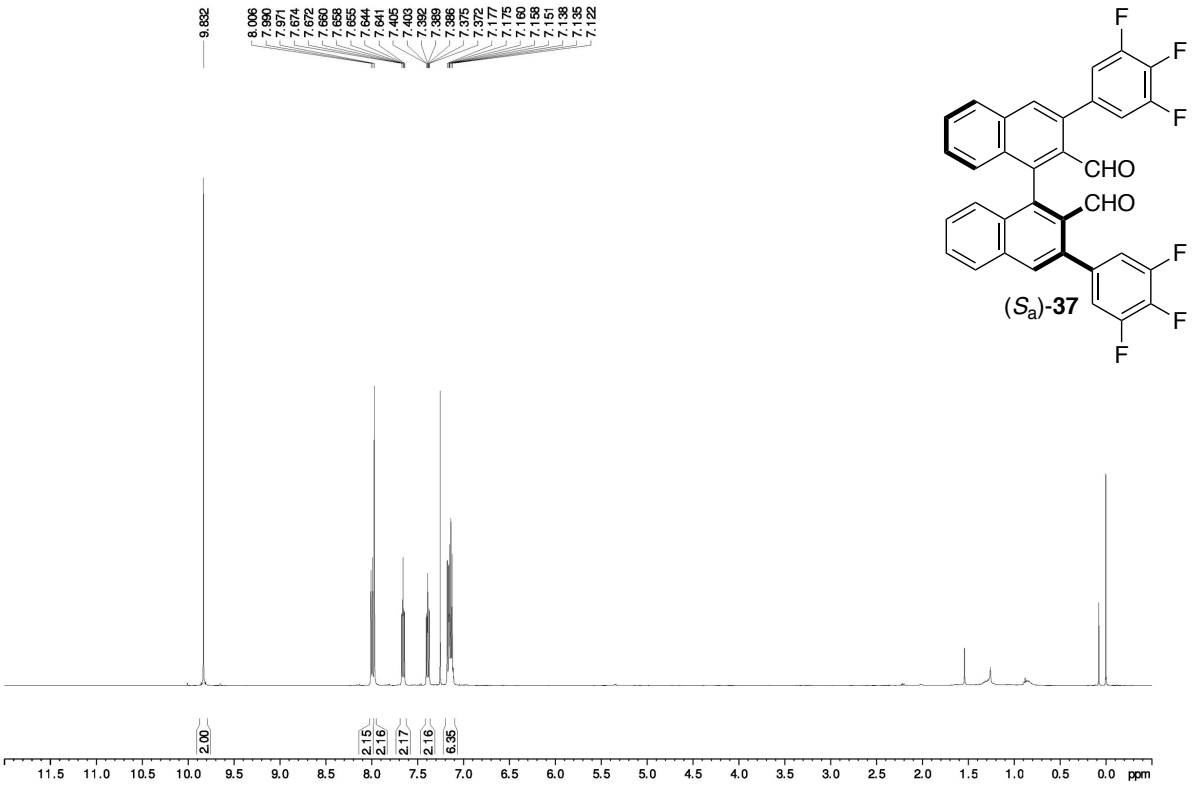


14h, ^{13}C NMR (126 MHz, $CDCl_3$)

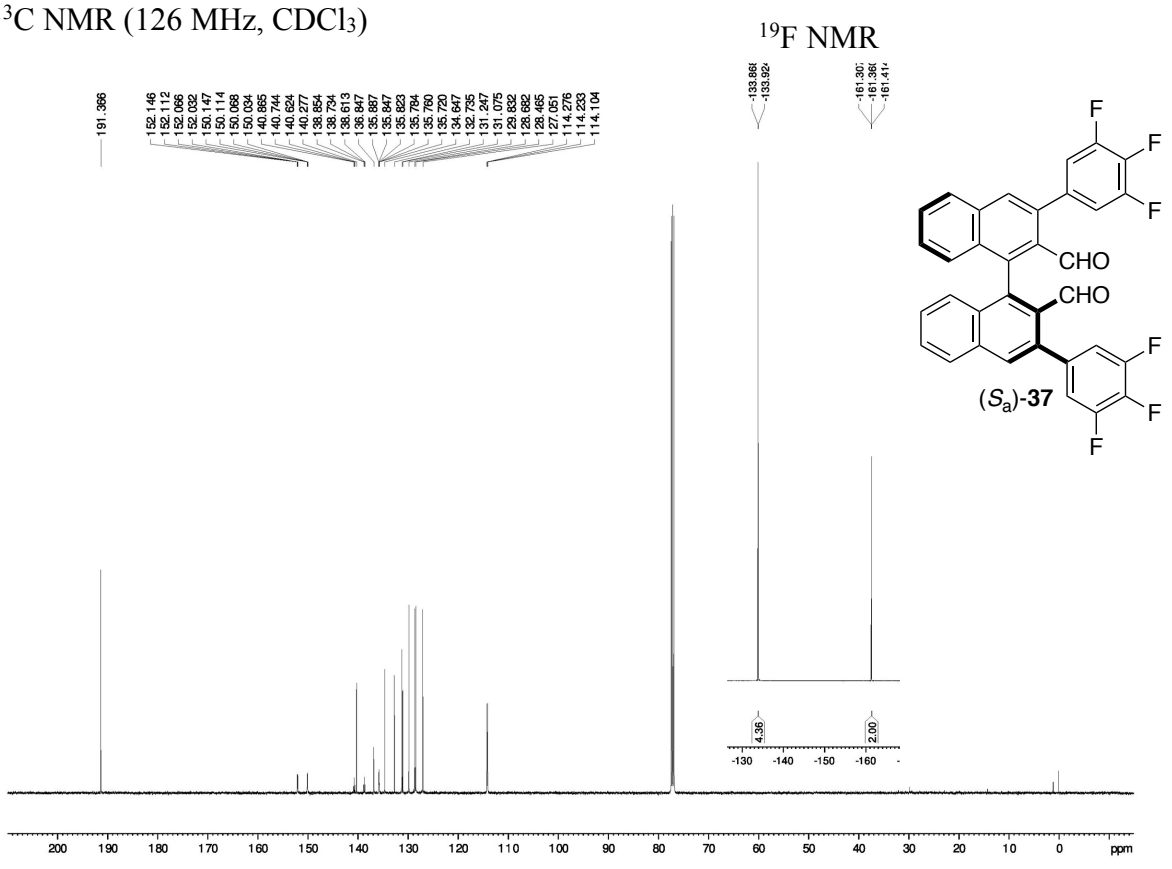
^{19}F NMR



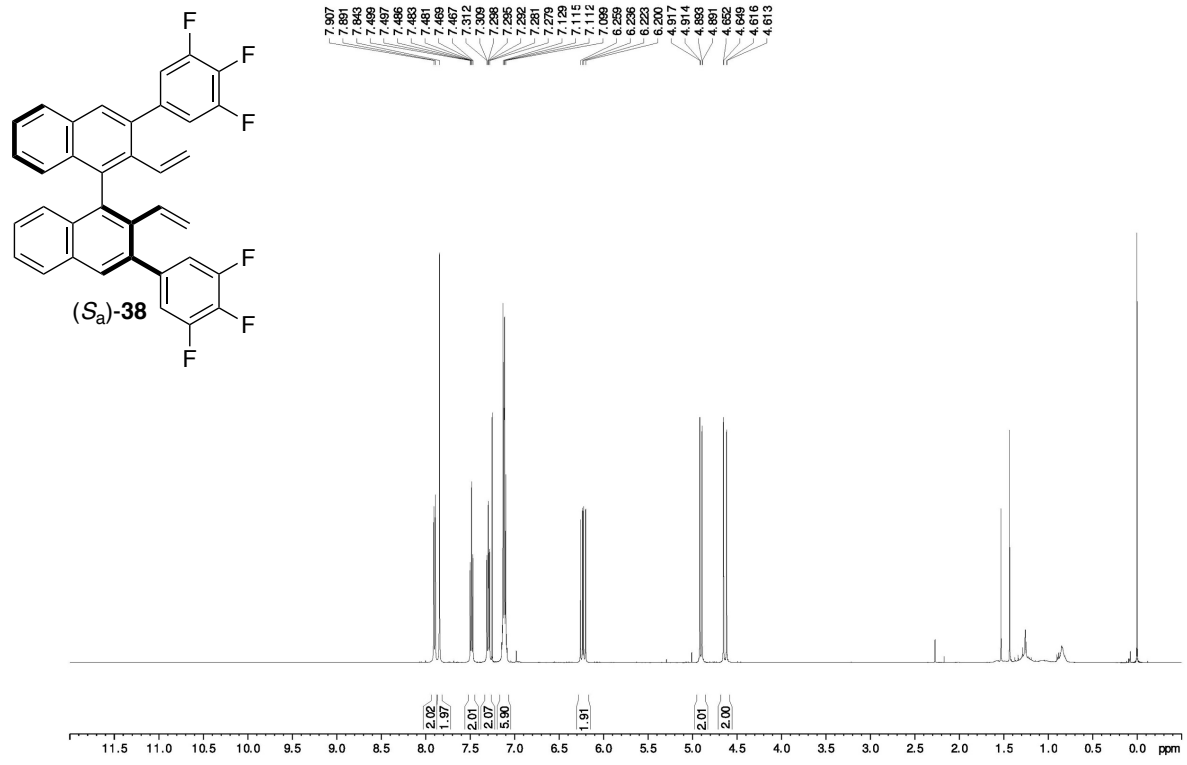
37, ^{1}H NMR (500 MHz, $CDCl_3$)



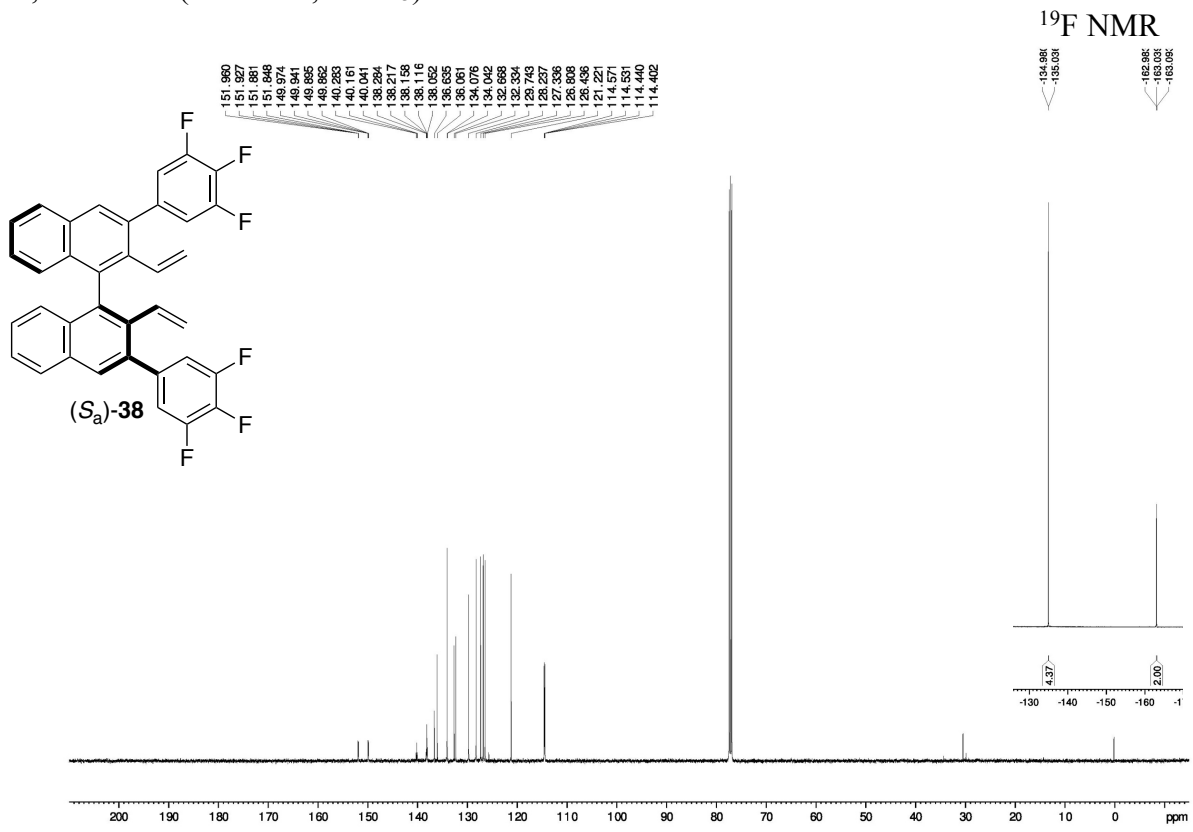
37, ^{13}C NMR (126 MHz, $CDCl_3$)



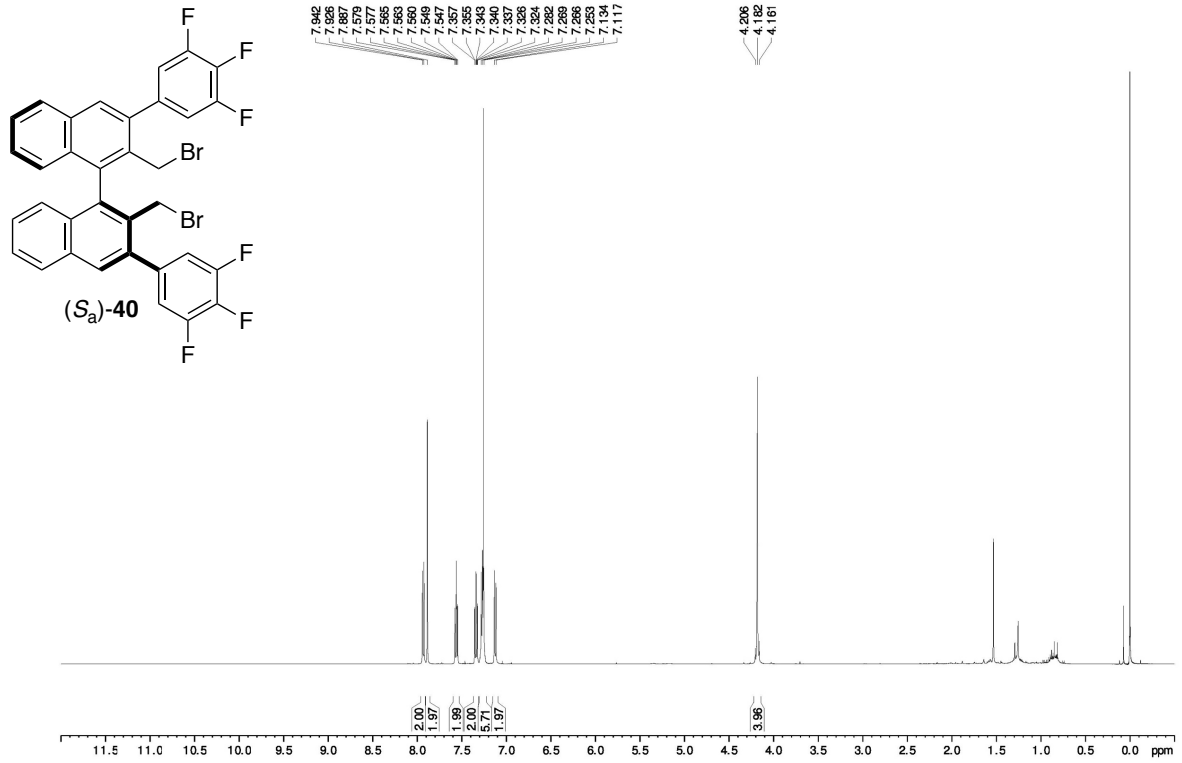
38, ^{1}H NMR (500 MHz, $CDCl_3$)



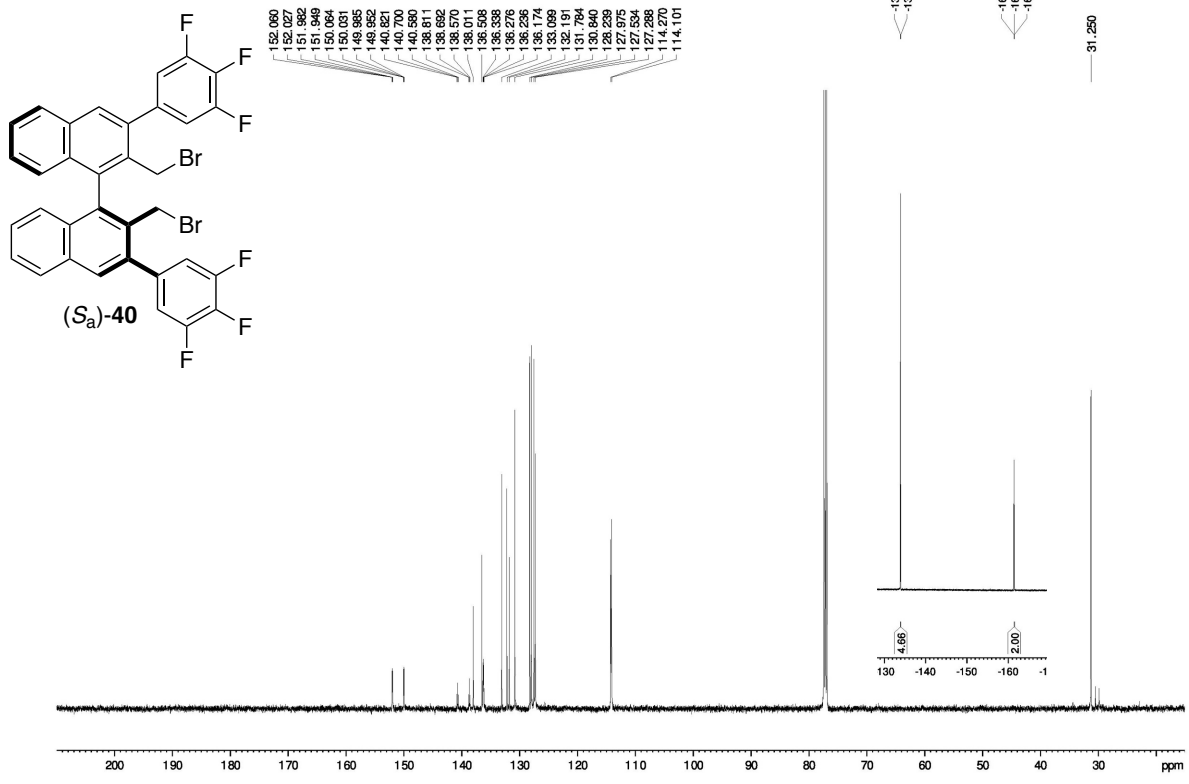
38, ^{13}C NMR (126 MHz, $CDCl_3$)



40, ^{1}H NMR (500 MHz, $CDCl_3$)

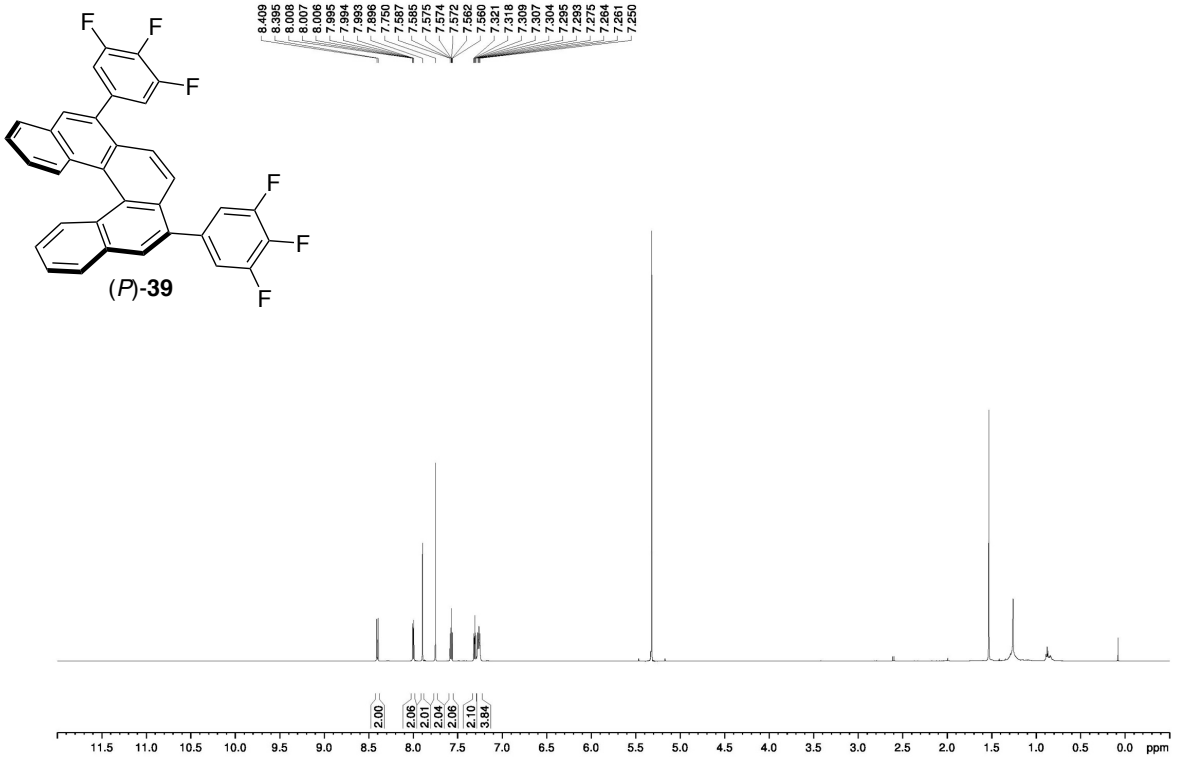


40, ^{13}C NMR (126 MHz, $CDCl_3$)

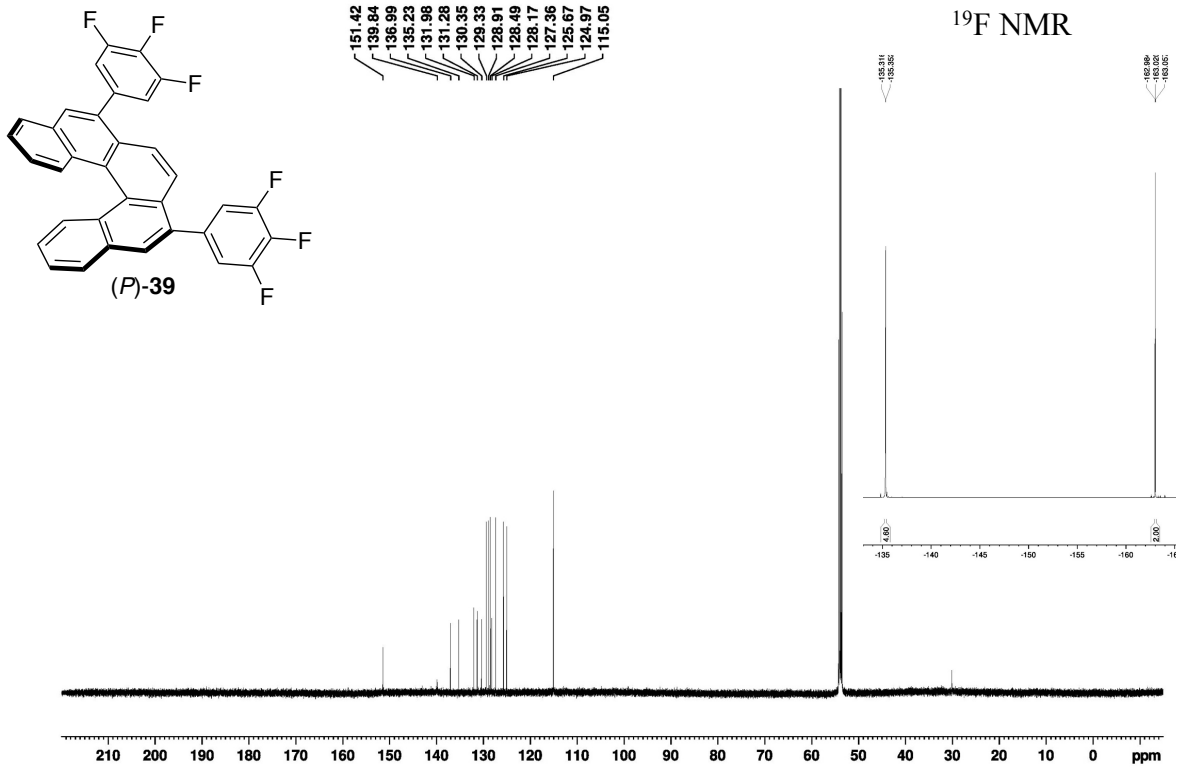


^{19}F NMR

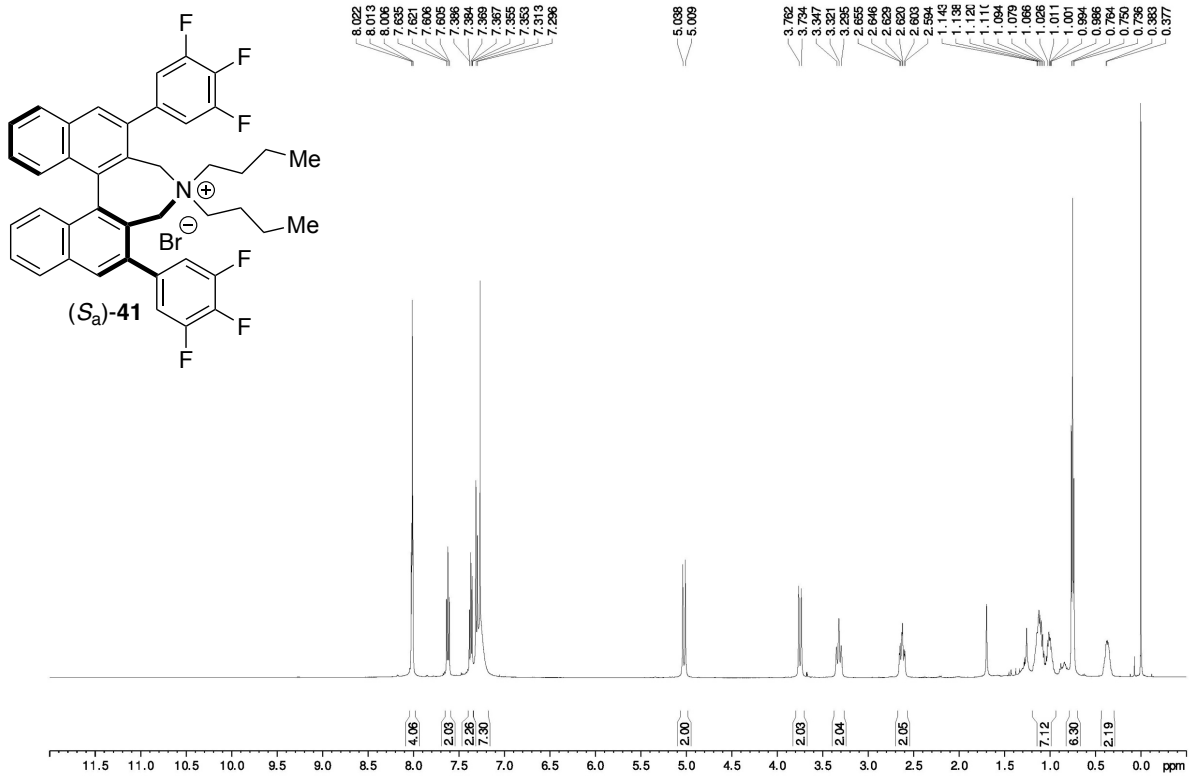
39, ^{1}H NMR (600 MHz, CD_2Cl_2)



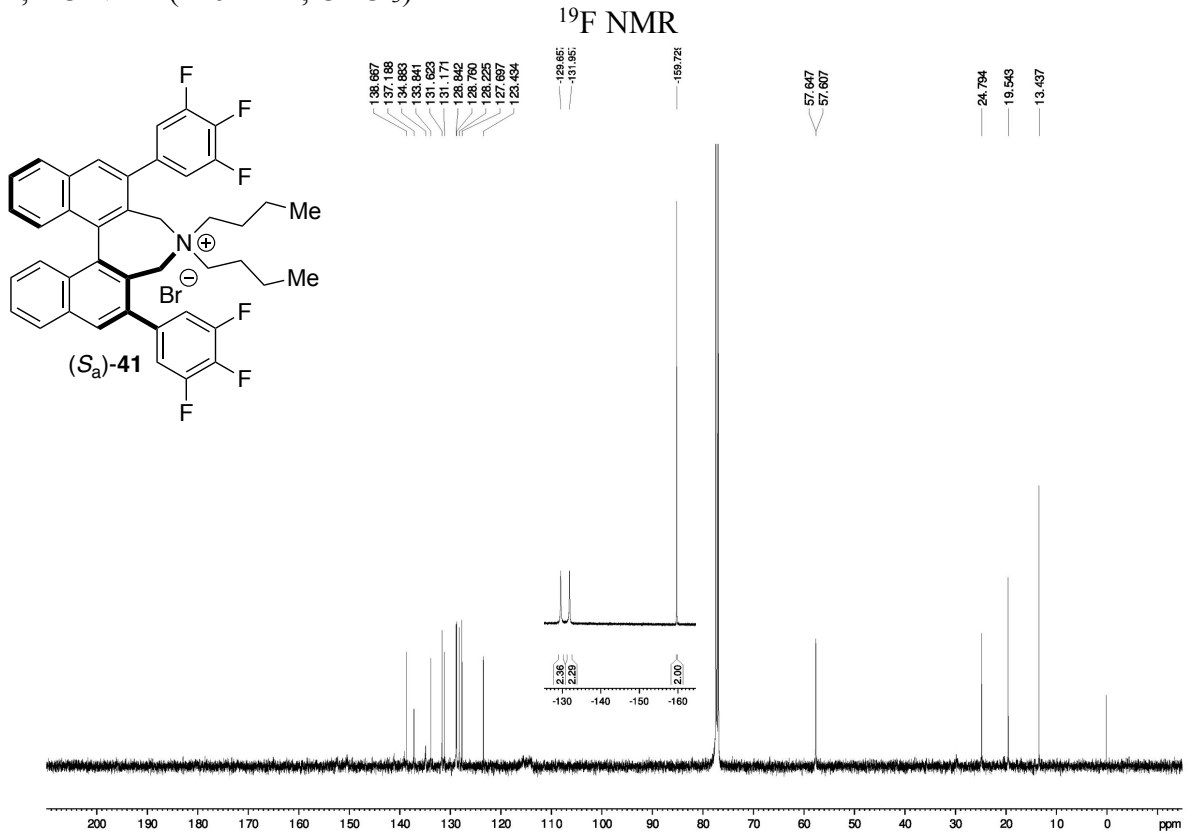
39, ^{13}C NMR-{^{1}H,^{19}F} (150 MHz, CD_2Cl_2)



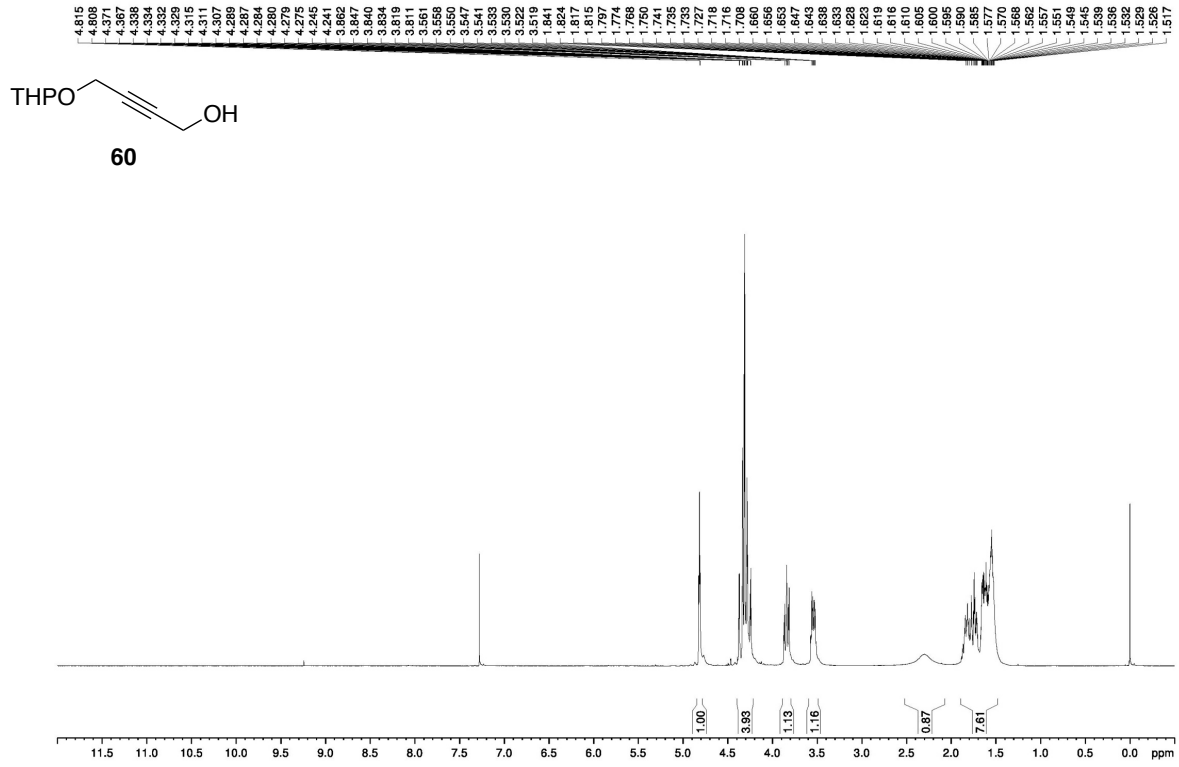
41, ^{1}H NMR (500 MHz, $CDCl_3$)



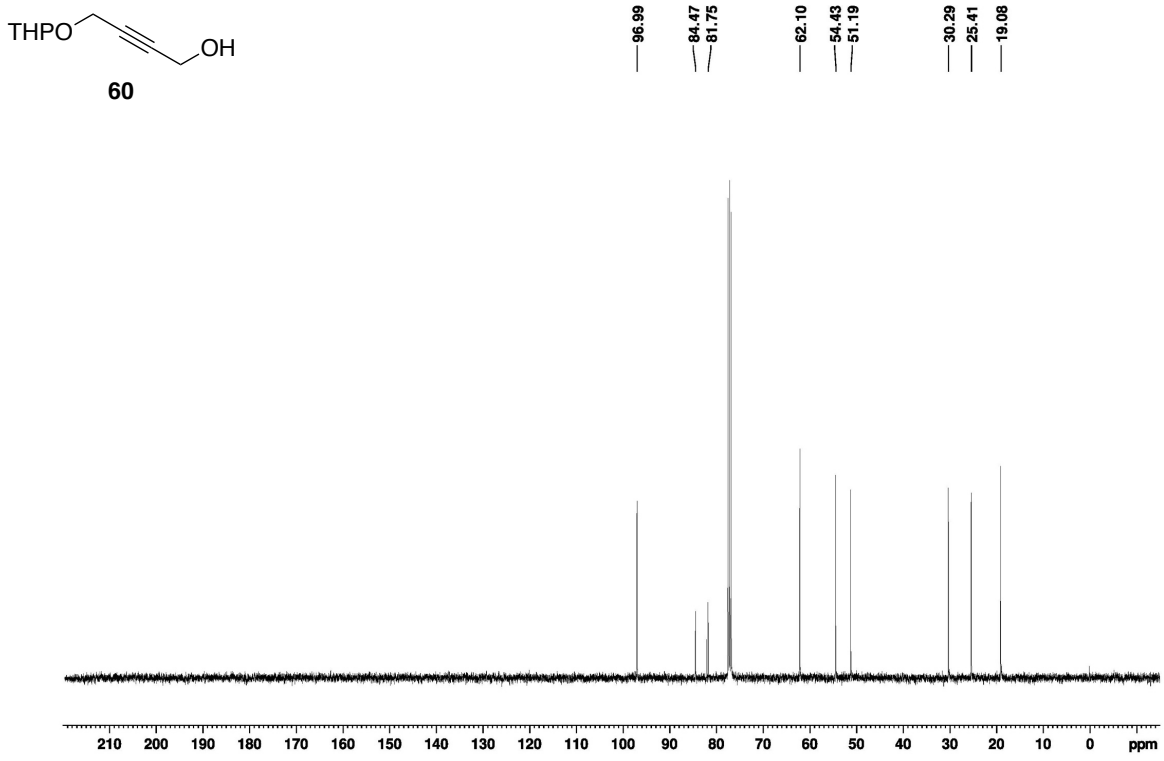
41, ^{13}C NMR (126 MHz, $CDCl_3$)



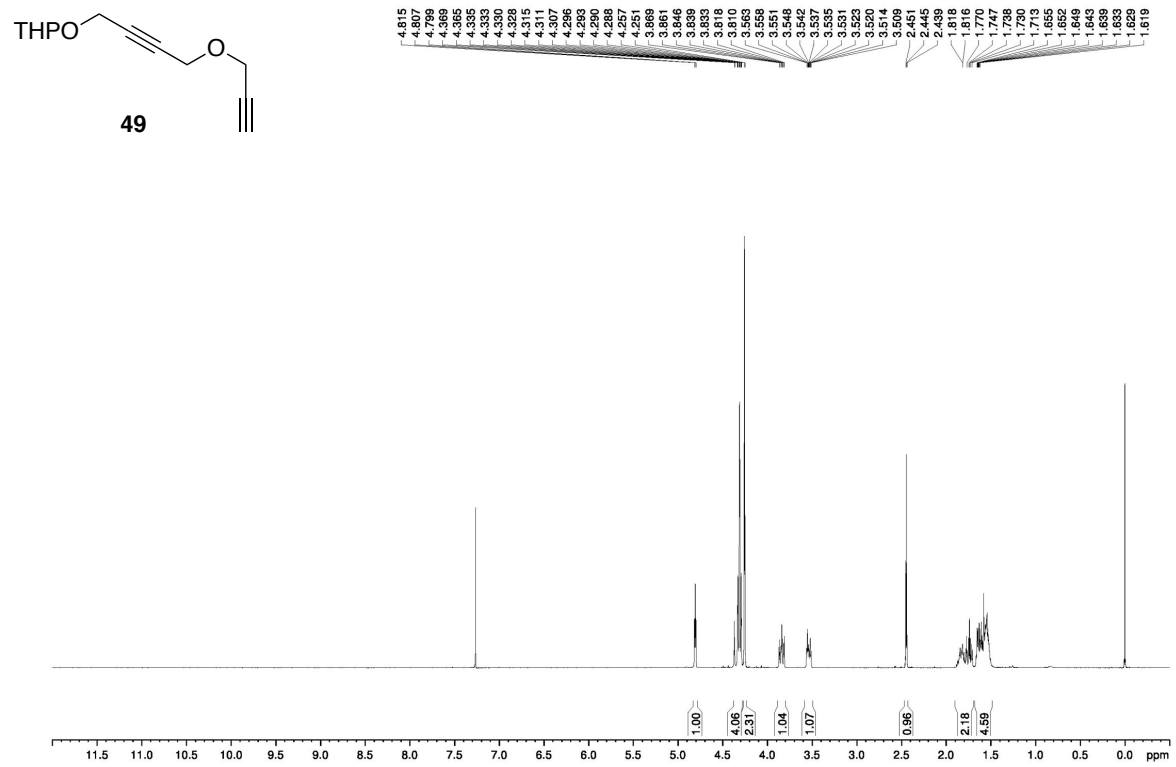
60, ^{1}H NMR (400 MHz, $CDCl_3$)



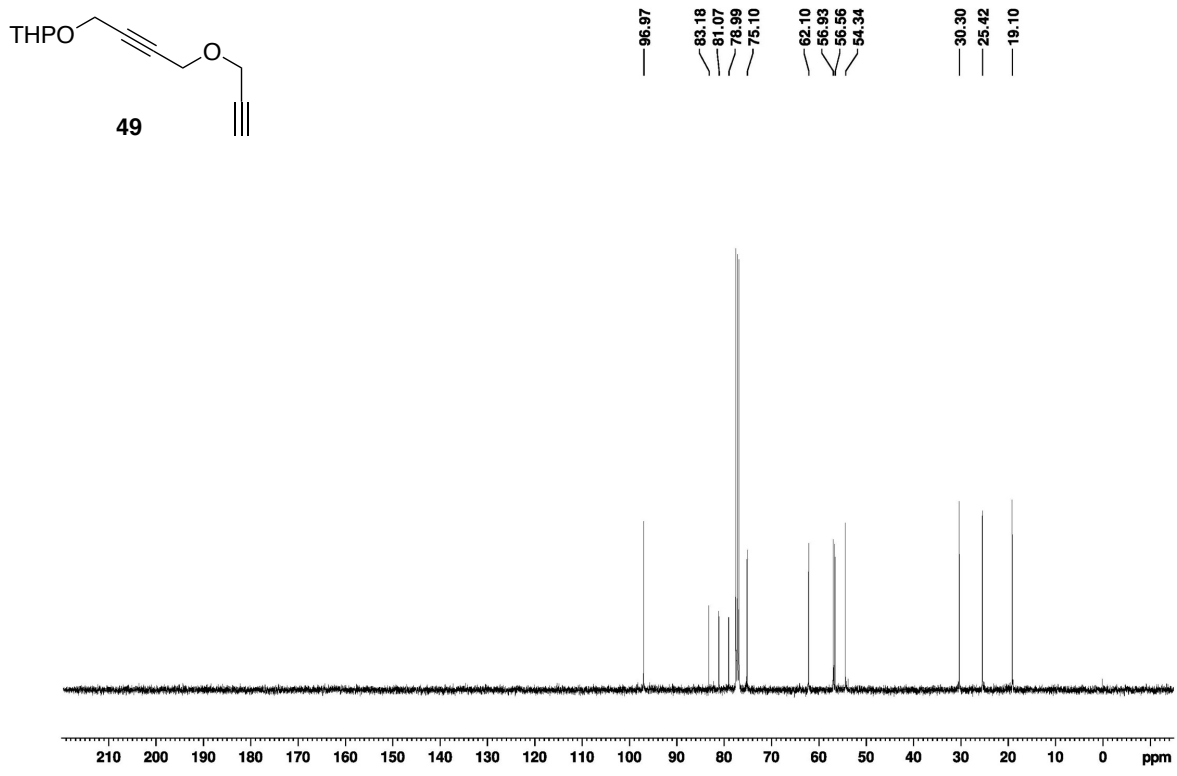
60, ^{13}C NMR (101 MHz, $CDCl_3$)



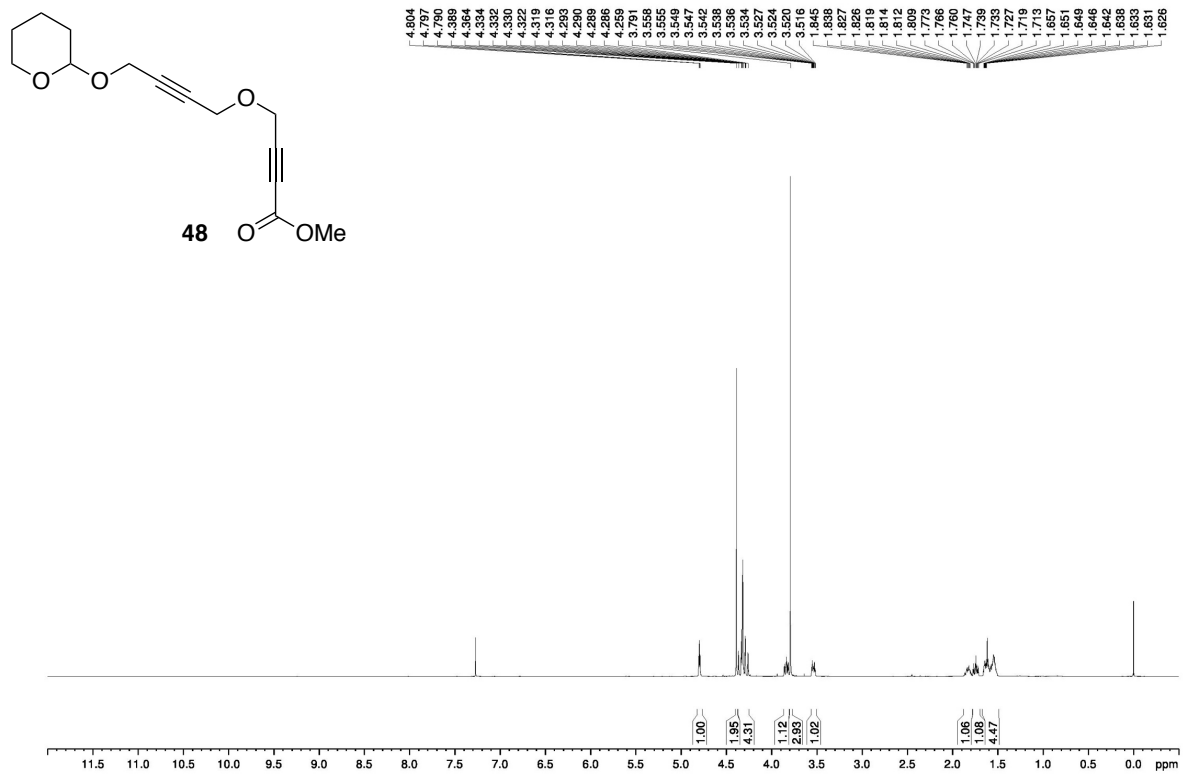
49, ^{1}H NMR (400 MHz, $CDCl_3$)



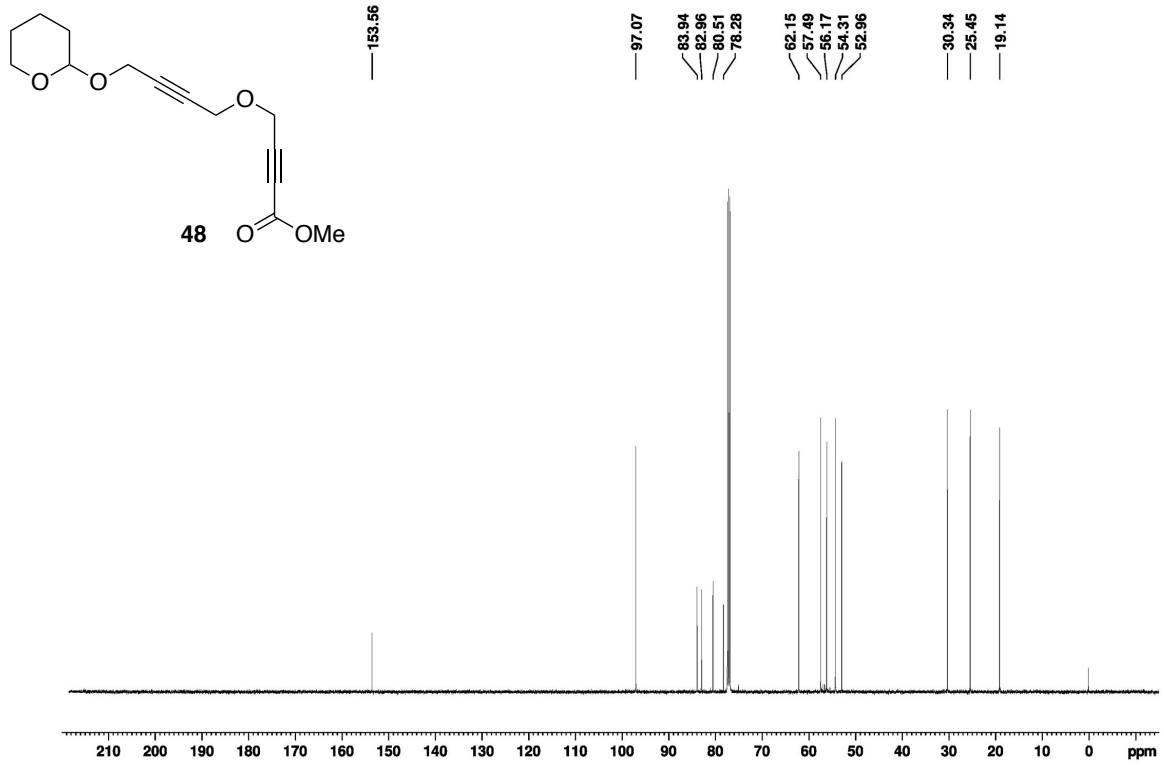
49, ^{13}C NMR (101 MHz, $CDCl_3$)



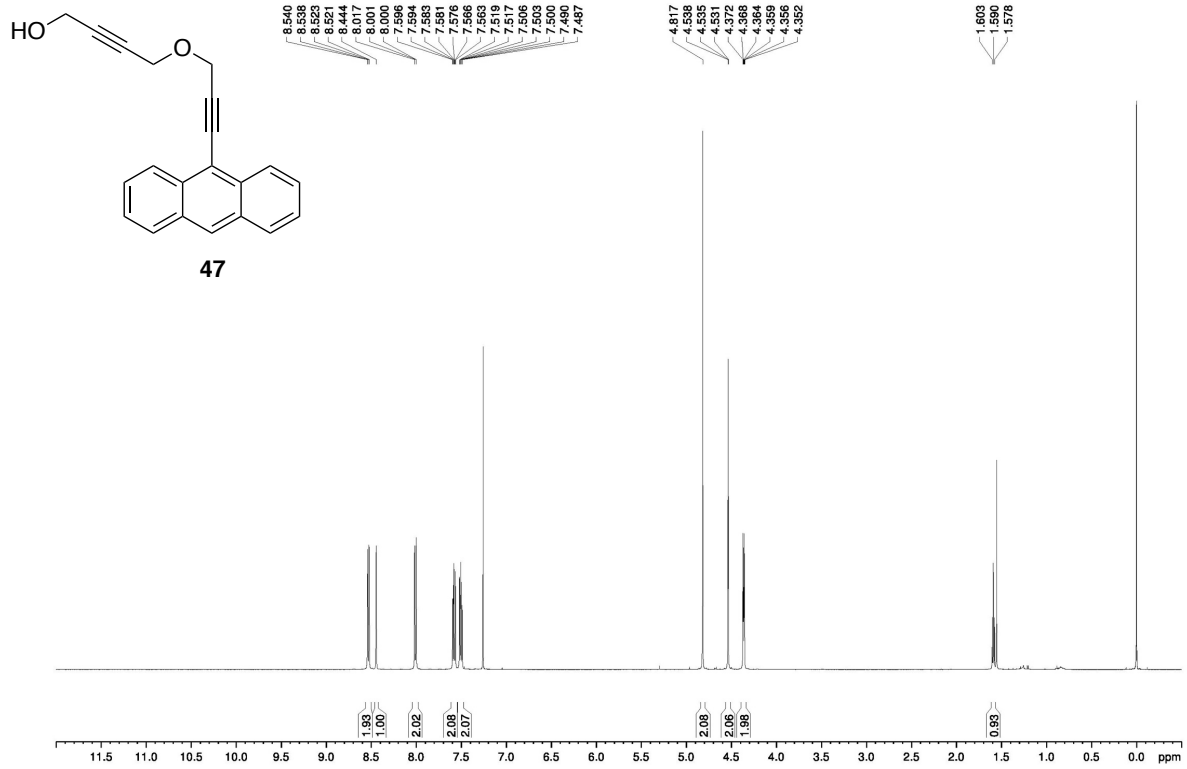
48, ^{1}H NMR (500 MHz, $CDCl_3$)



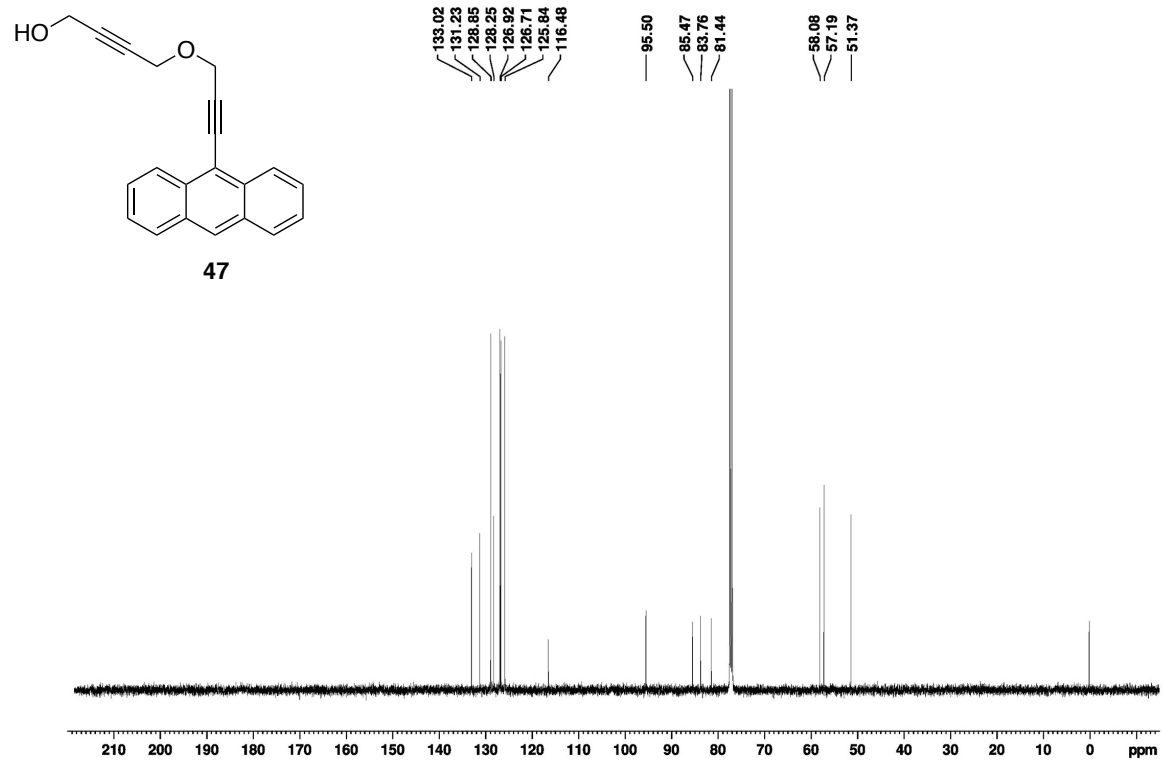
48, ^{13}C NMR (126 MHz, $CDCl_3$)



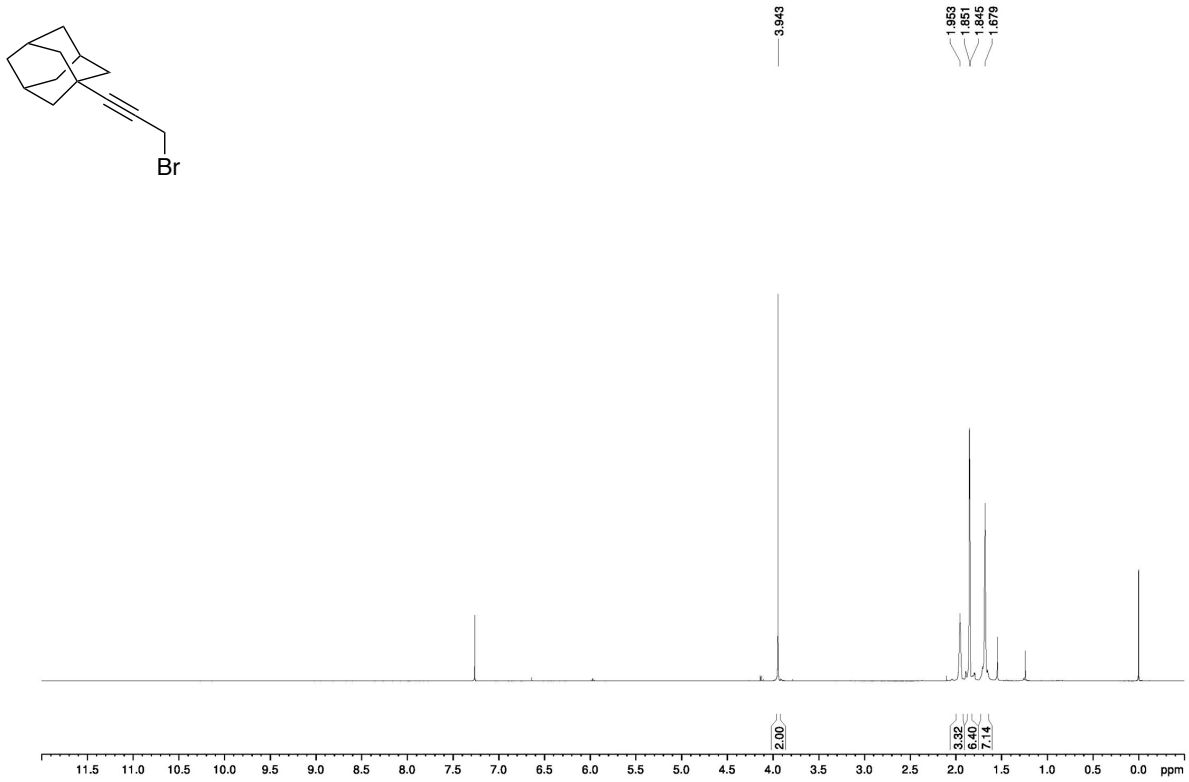
47, ^{1}H NMR (500 MHz, $CDCl_3$)



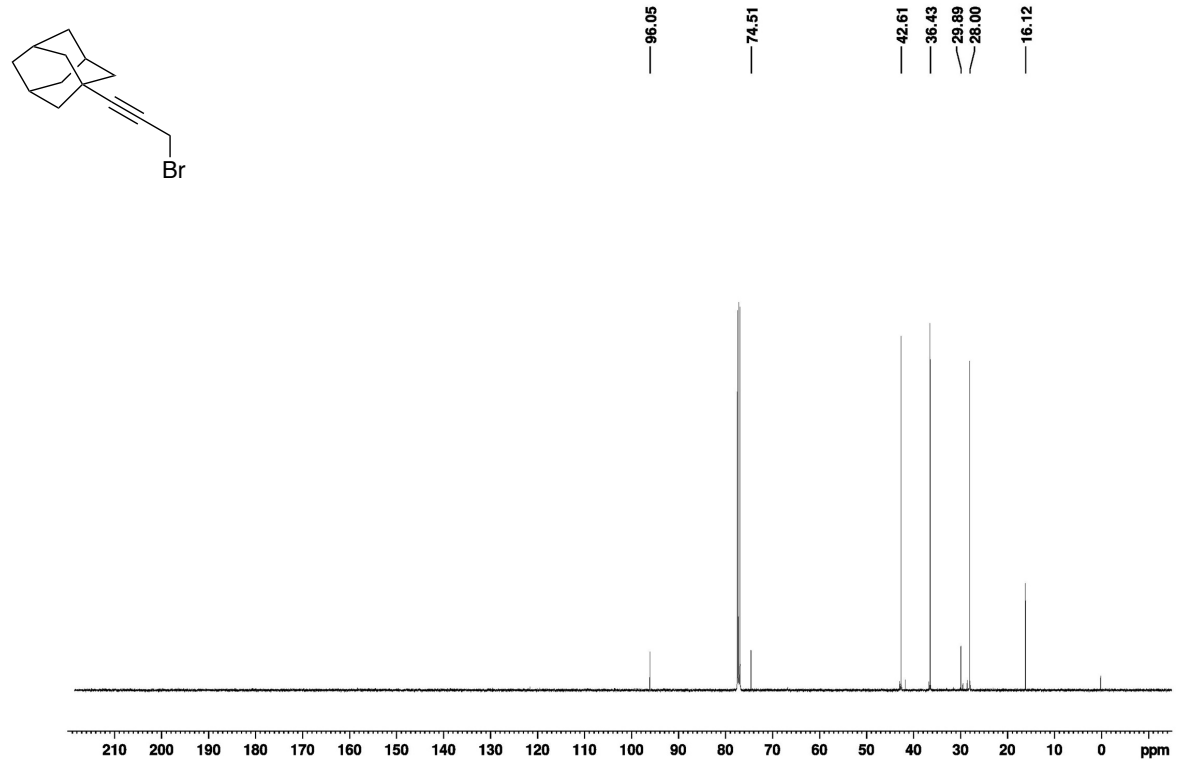
47, ^{13}C NMR (126 MHz, $CDCl_3$)



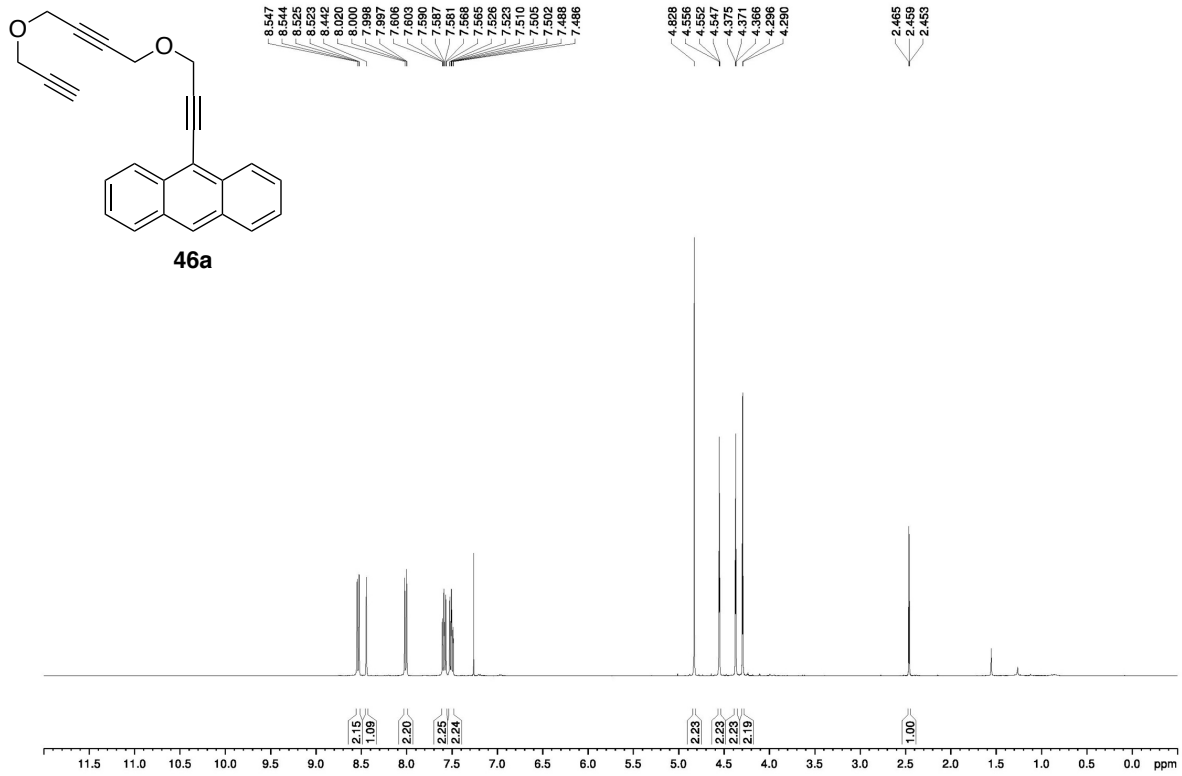
1-(3-Bromoprop-1-yn-1-yl)adamantane, ^{1}H NMR (500 MHz, $CDCl_3$)



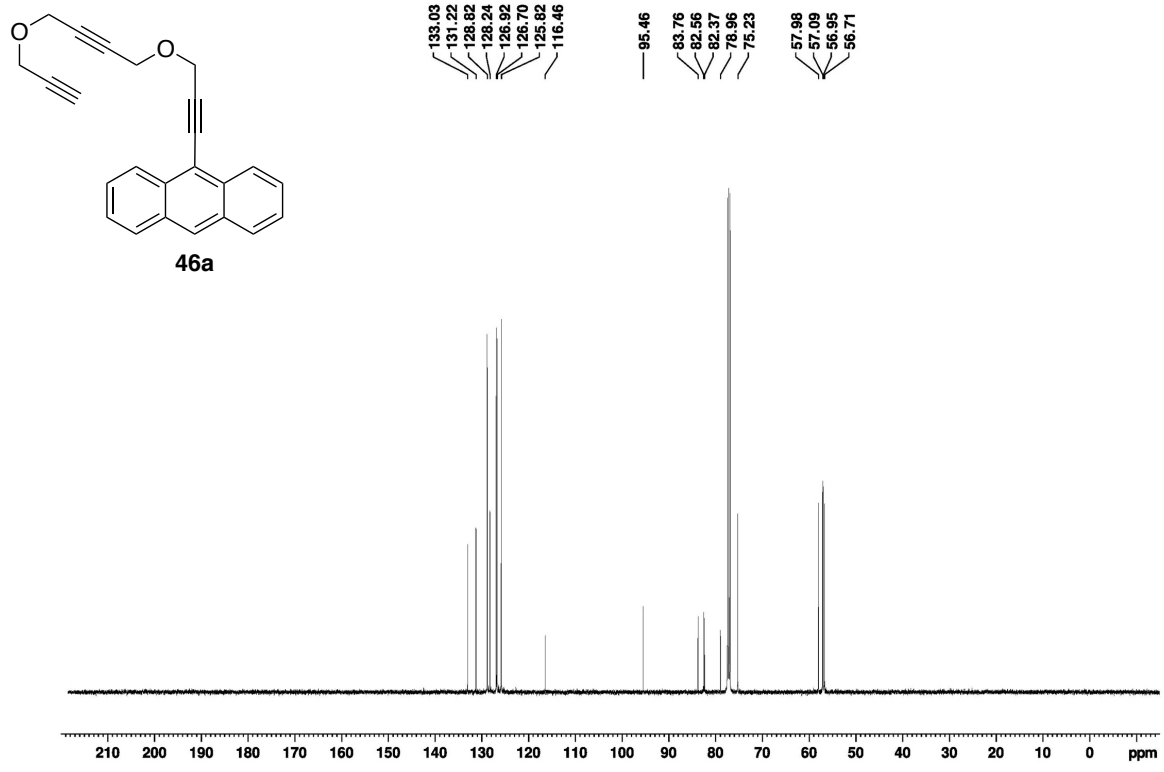
1-(3-Bromoprop-1-yn-1-yl)adamantane, ^{13}C NMR (126 MHz, $CDCl_3$)



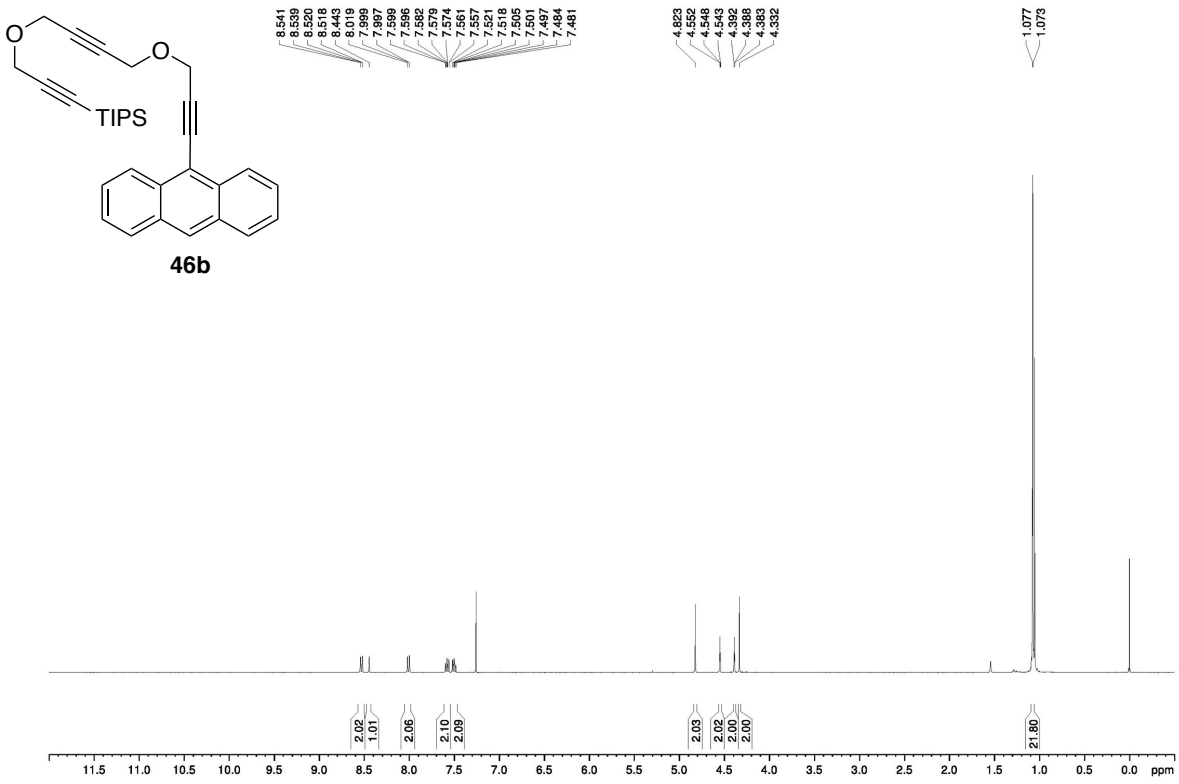
46a, ^{1}H NMR (400 MHz, $CDCl_3$)



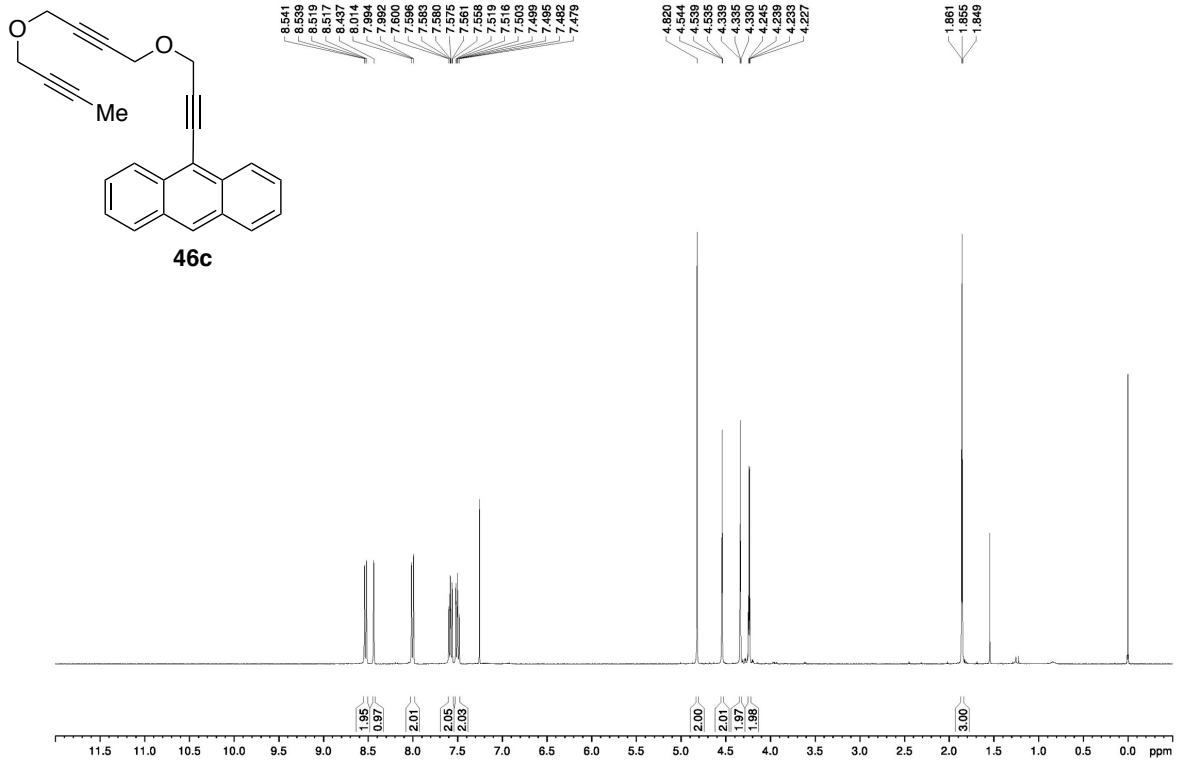
46a, ^{13}C NMR (126 MHz, $CDCl_3$)



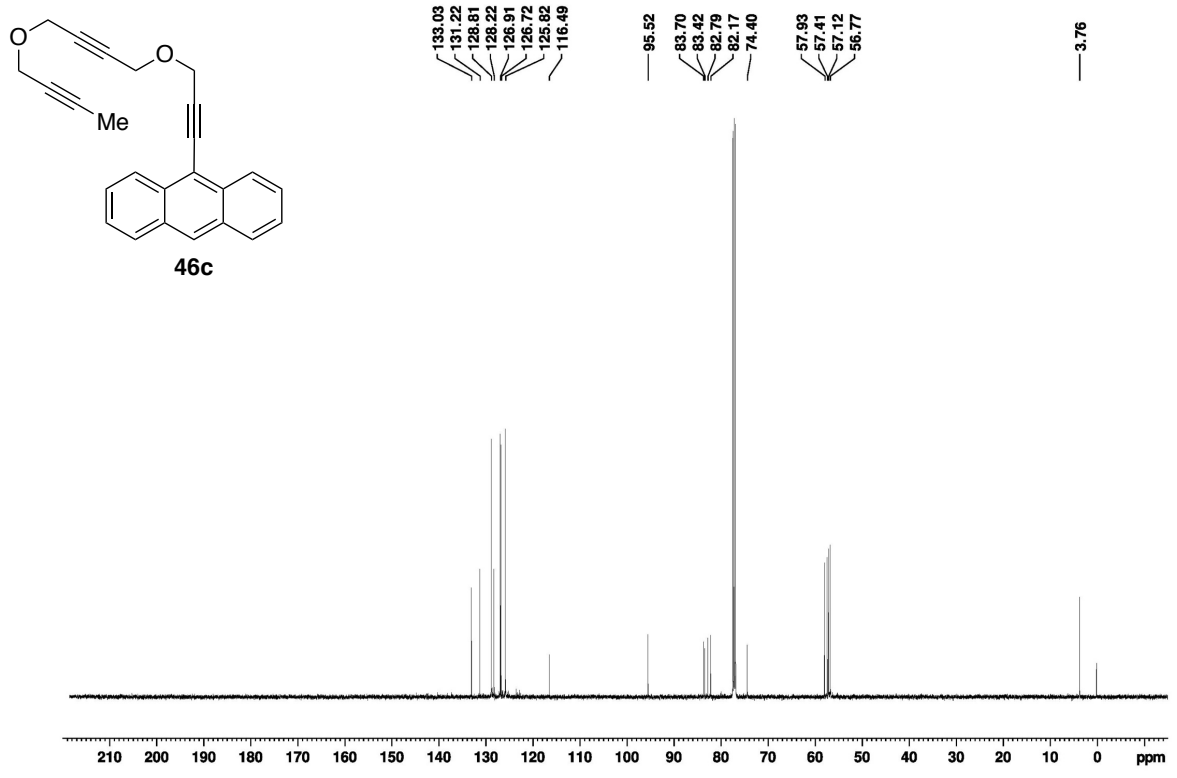
46b, ^{1}H NMR (400 MHz, $CDCl_3$)



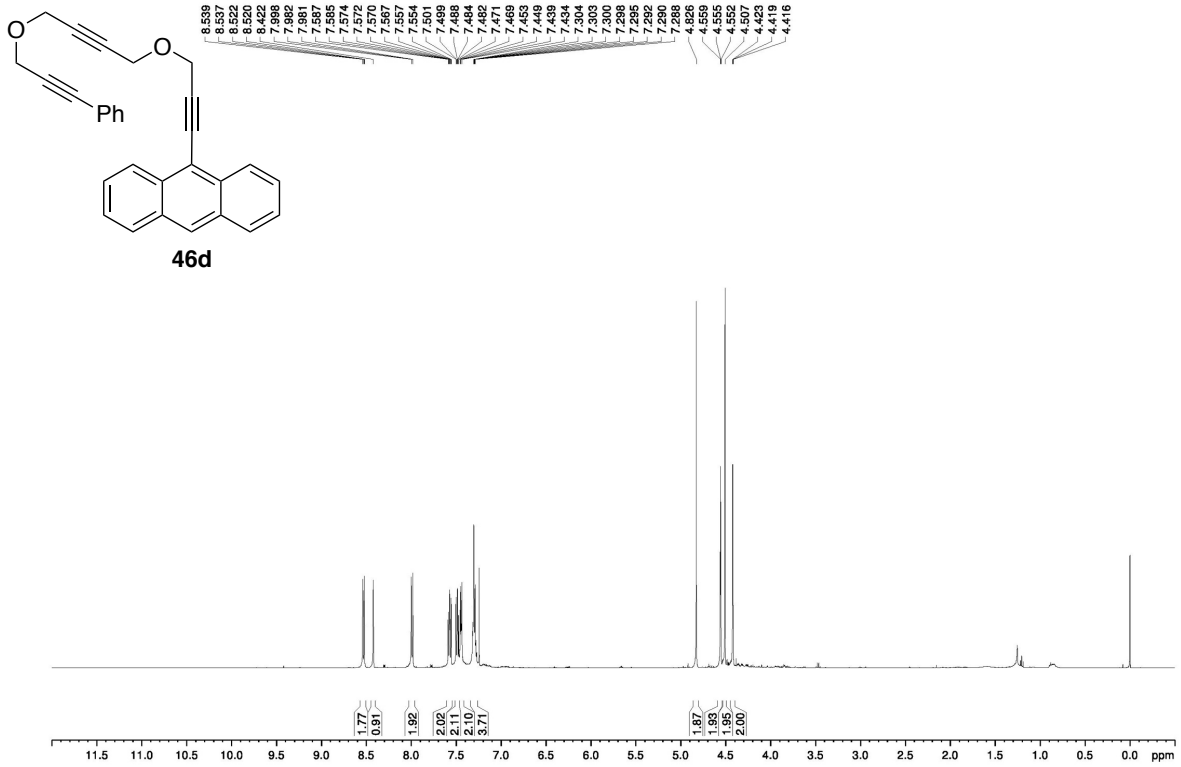
46c, ^{1}H NMR (400 MHz, $CDCl_3$)



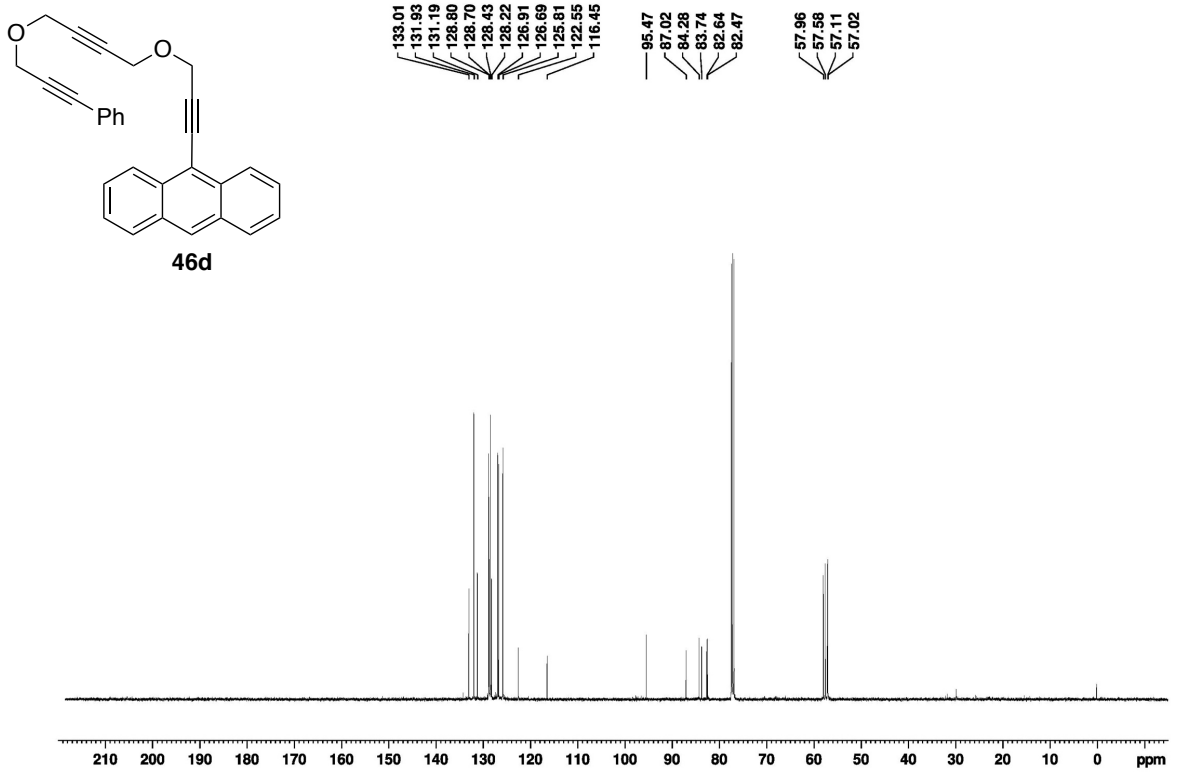
46c, ^{13}C NMR (126 MHz, $CDCl_3$)



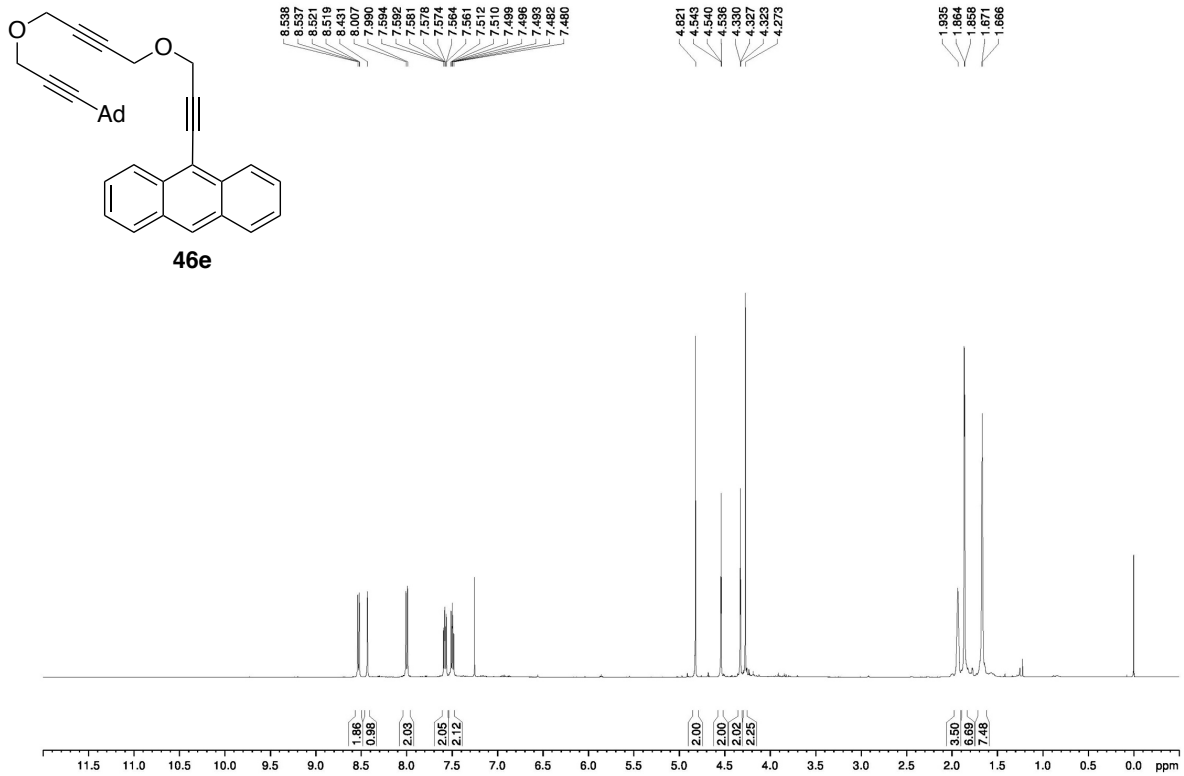
46d, ^{1}H NMR (500 MHz, $CDCl_3$)



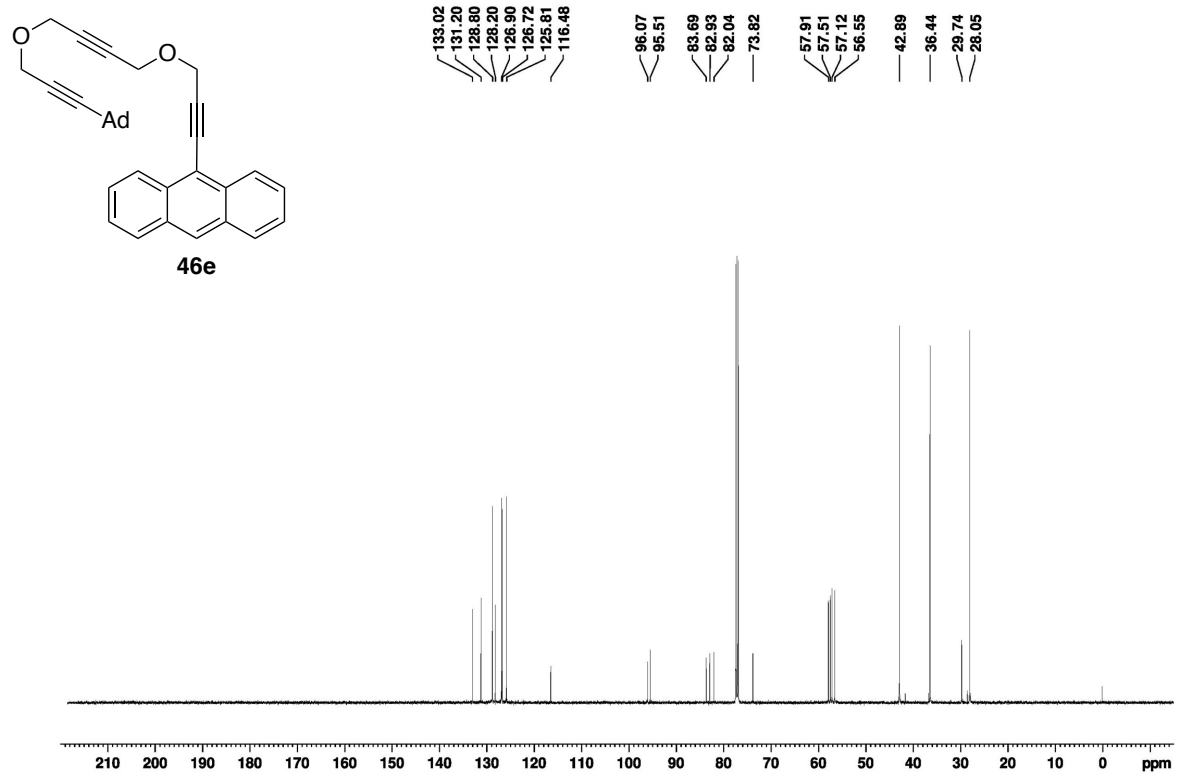
46d, ^{13}C NMR (126 MHz, $CDCl_3$)



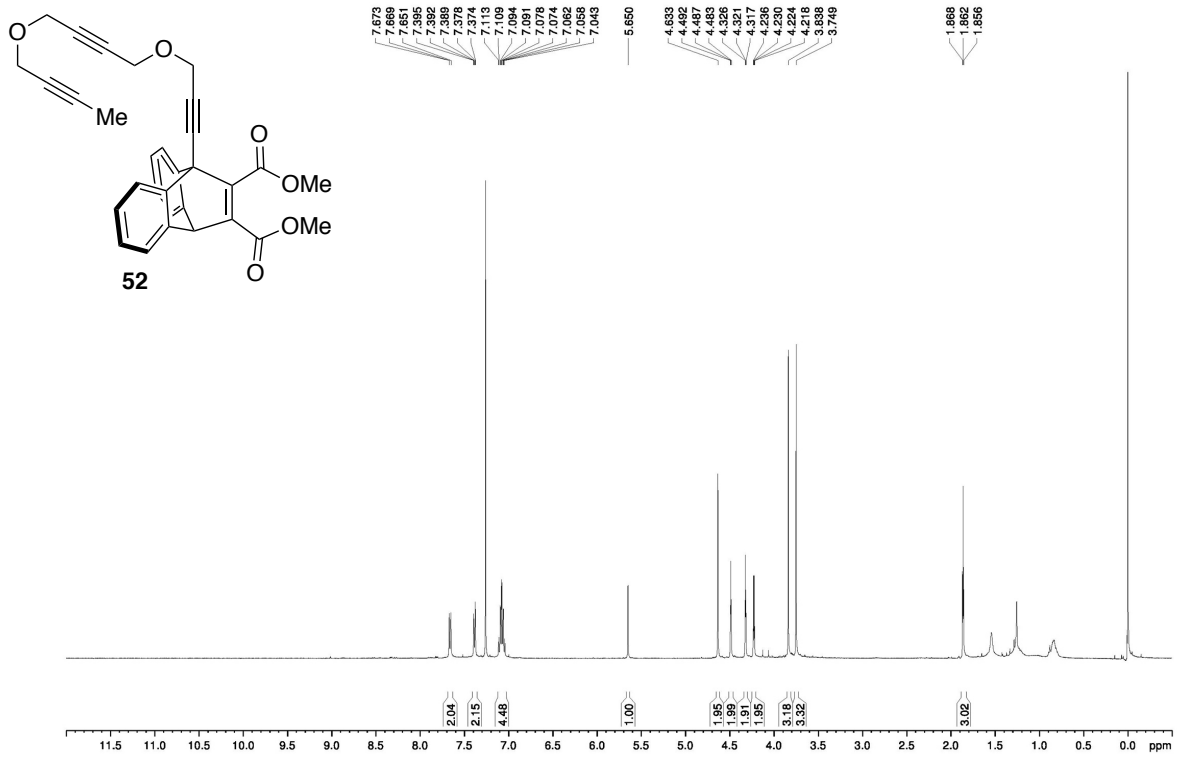
46e, ^{1}H NMR (500 MHz, $CDCl_3$)



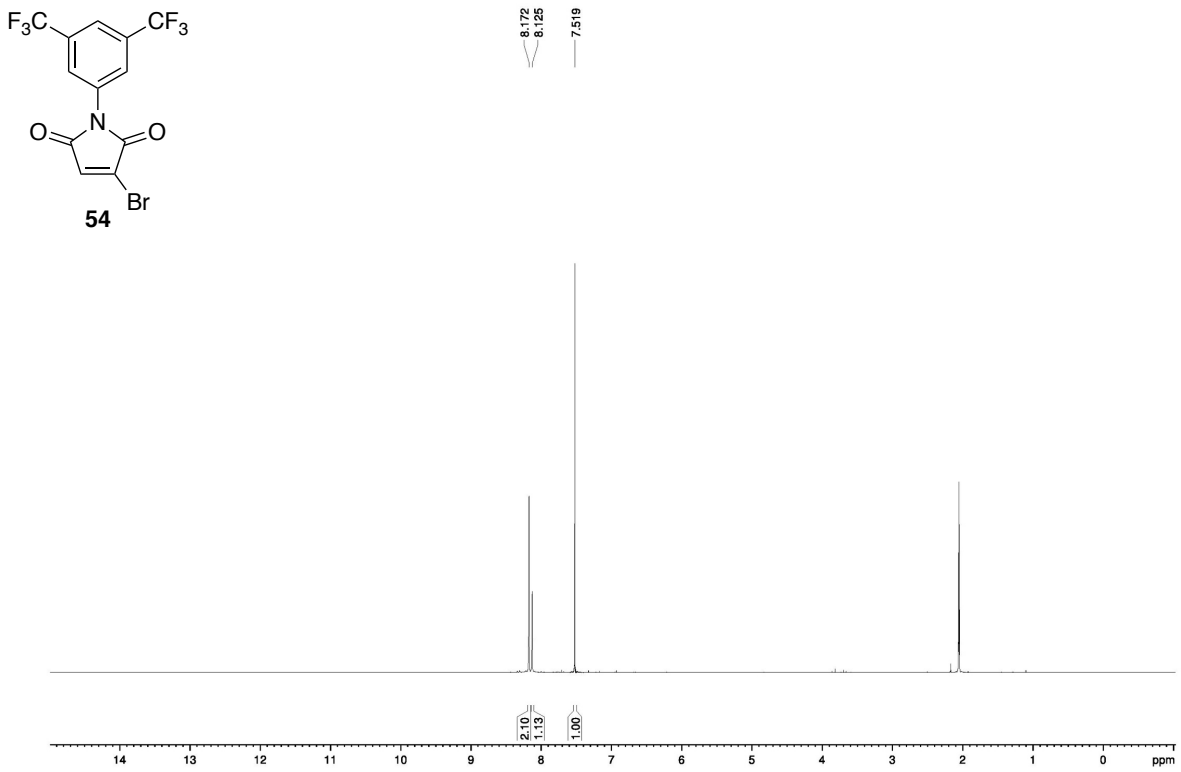
46e, ^{13}C NMR (126 MHz, $CDCl_3$)



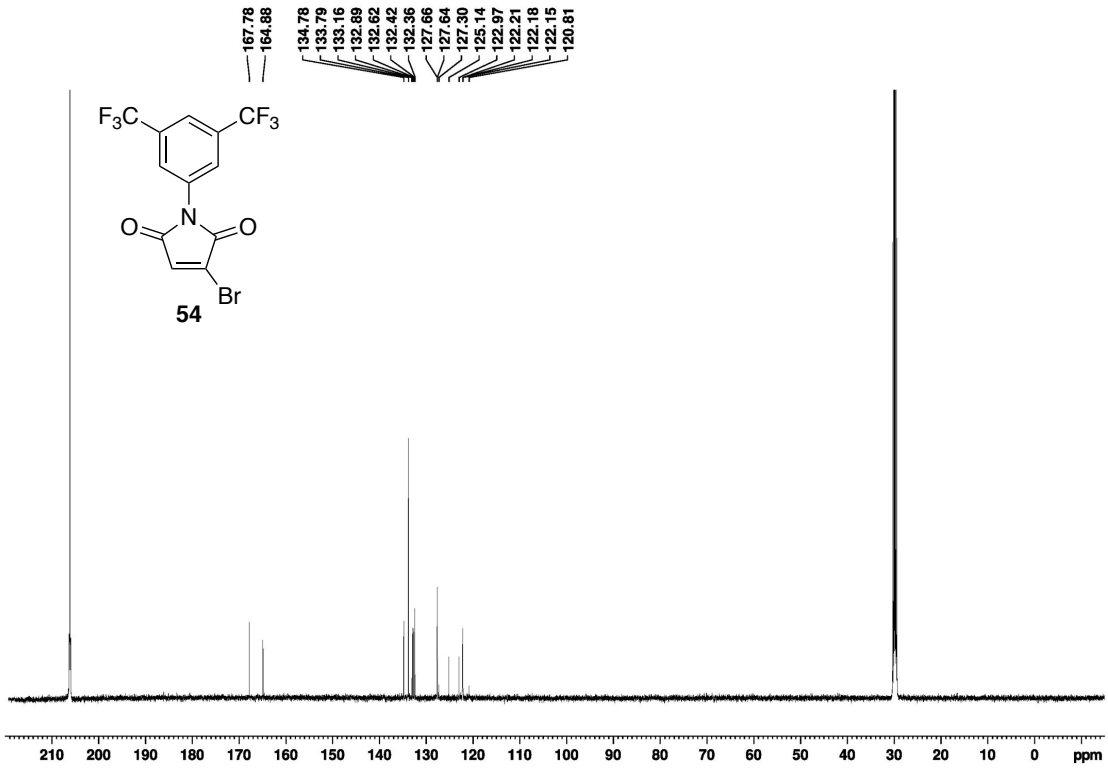
52, ^{1}H NMR (500 MHz, $CDCl_3$)



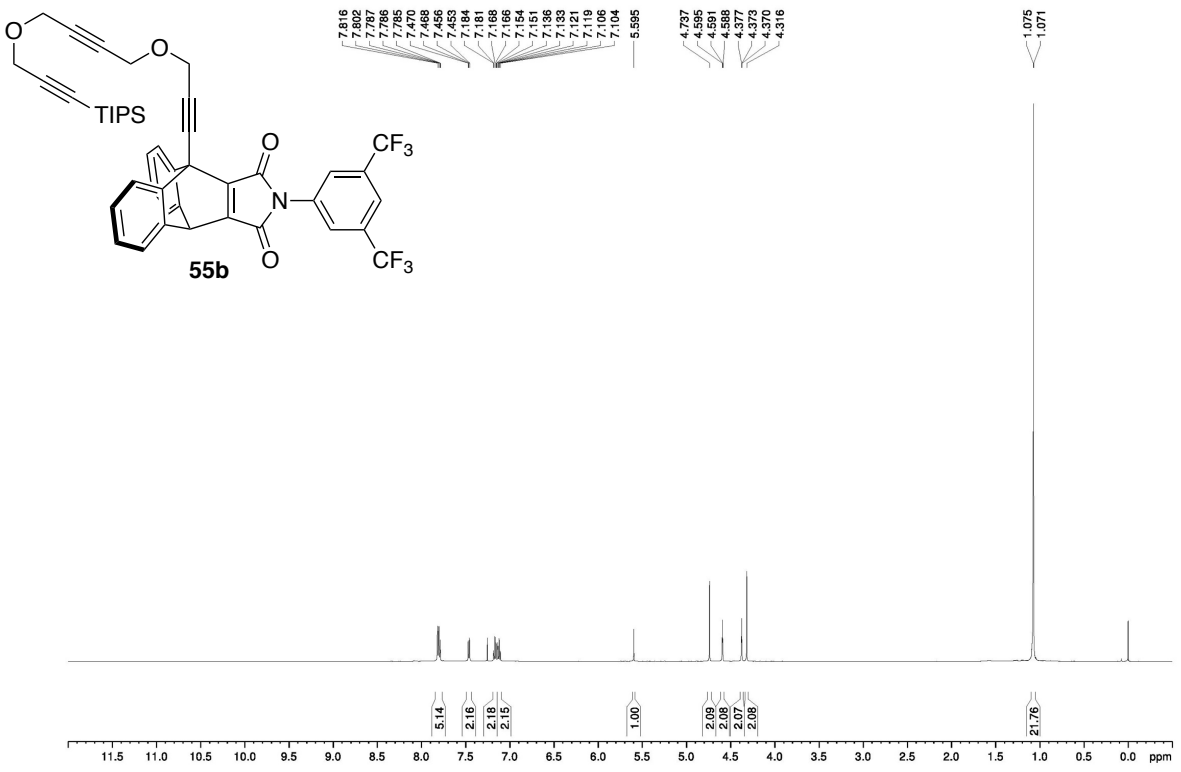
54, ^{1}H NMR (500 MHz, $(CD_3)_2CO$)



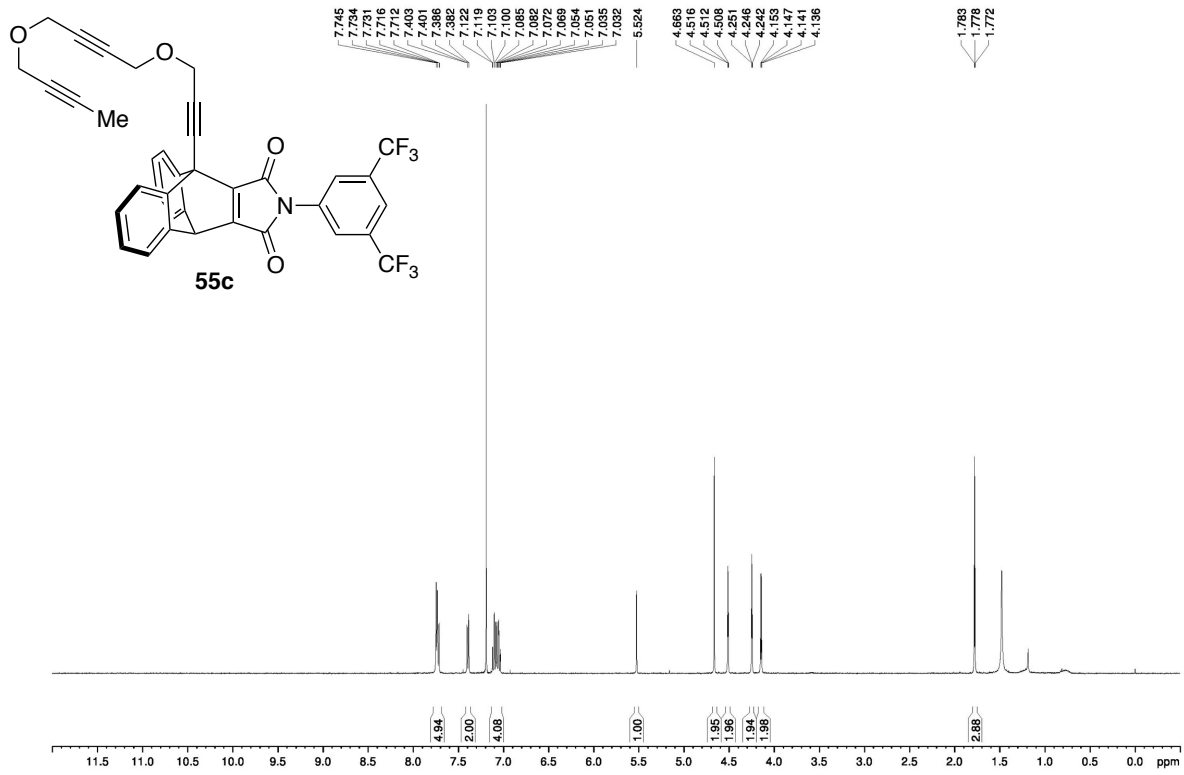
54, ^{13}C NMR (126 MHz, $(CD_3)_2CO$)



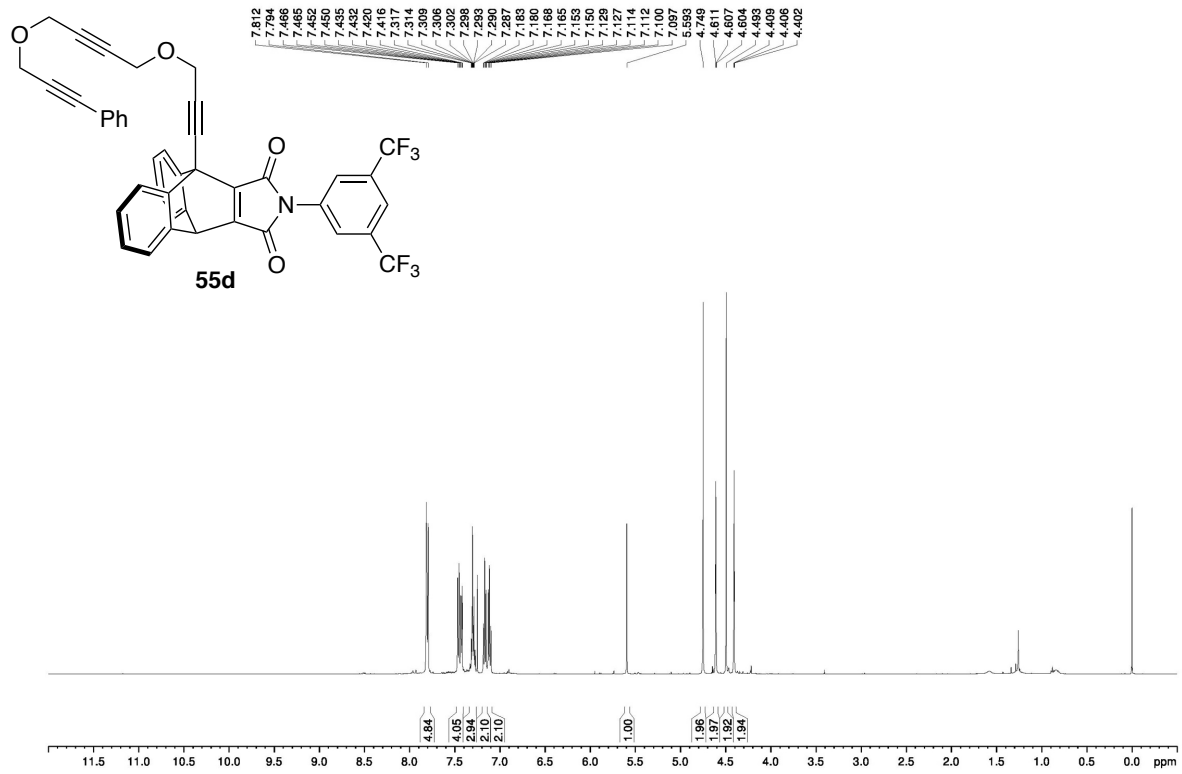
55b, ^{1}H NMR (500 MHz, $CDCl_3$)



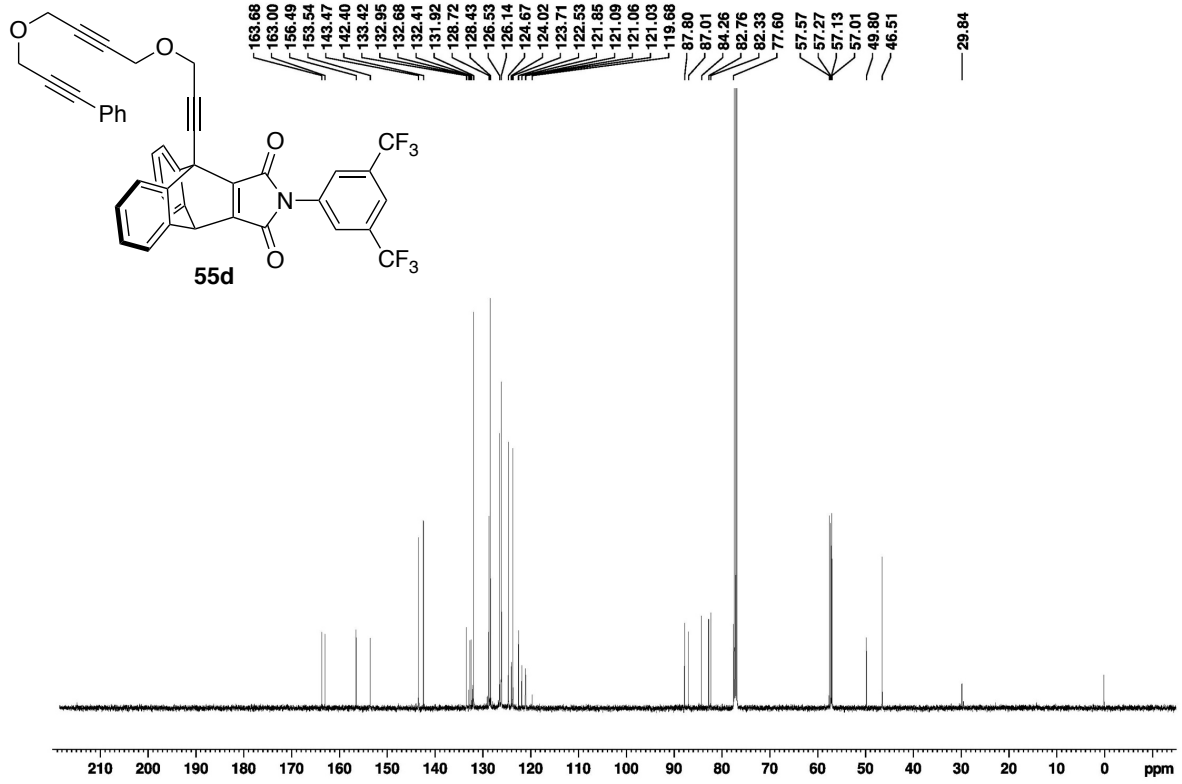
55c, ^{1}H NMR (400 MHz, $CDCl_3$)



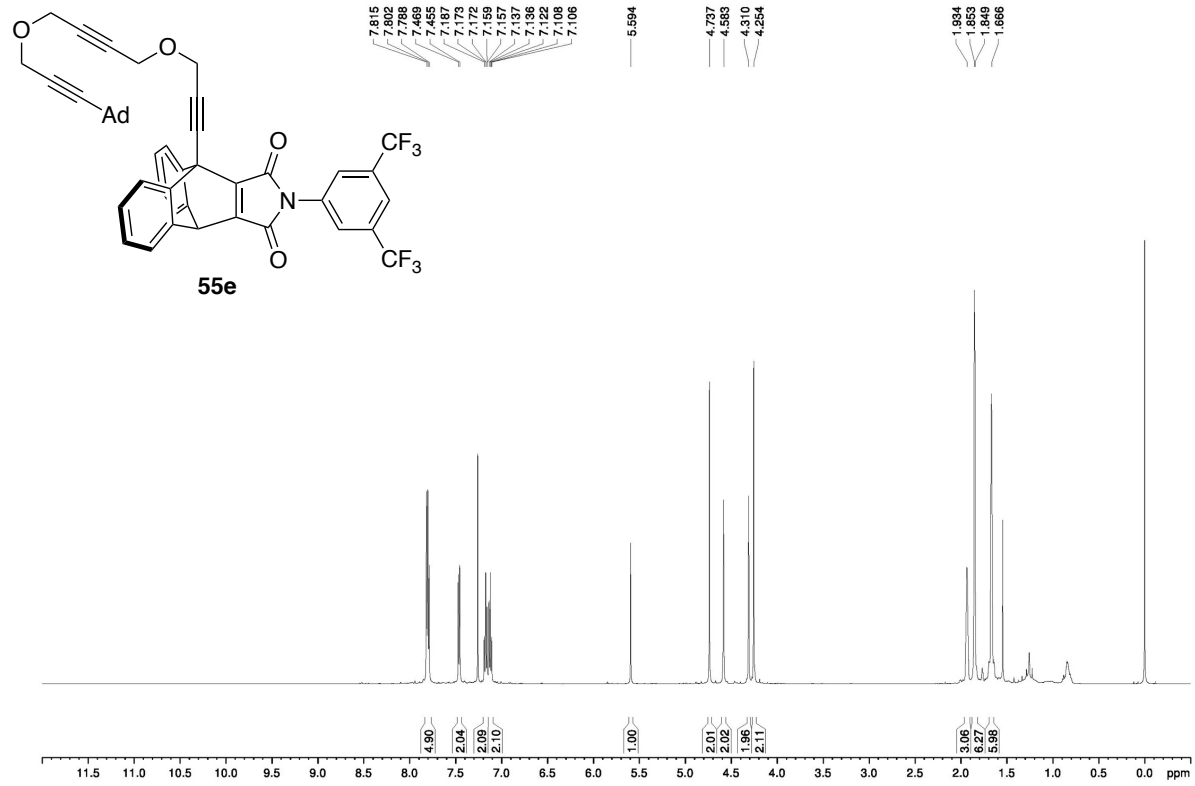
55d, ^{1}H NMR (500 MHz, $CDCl_3$)



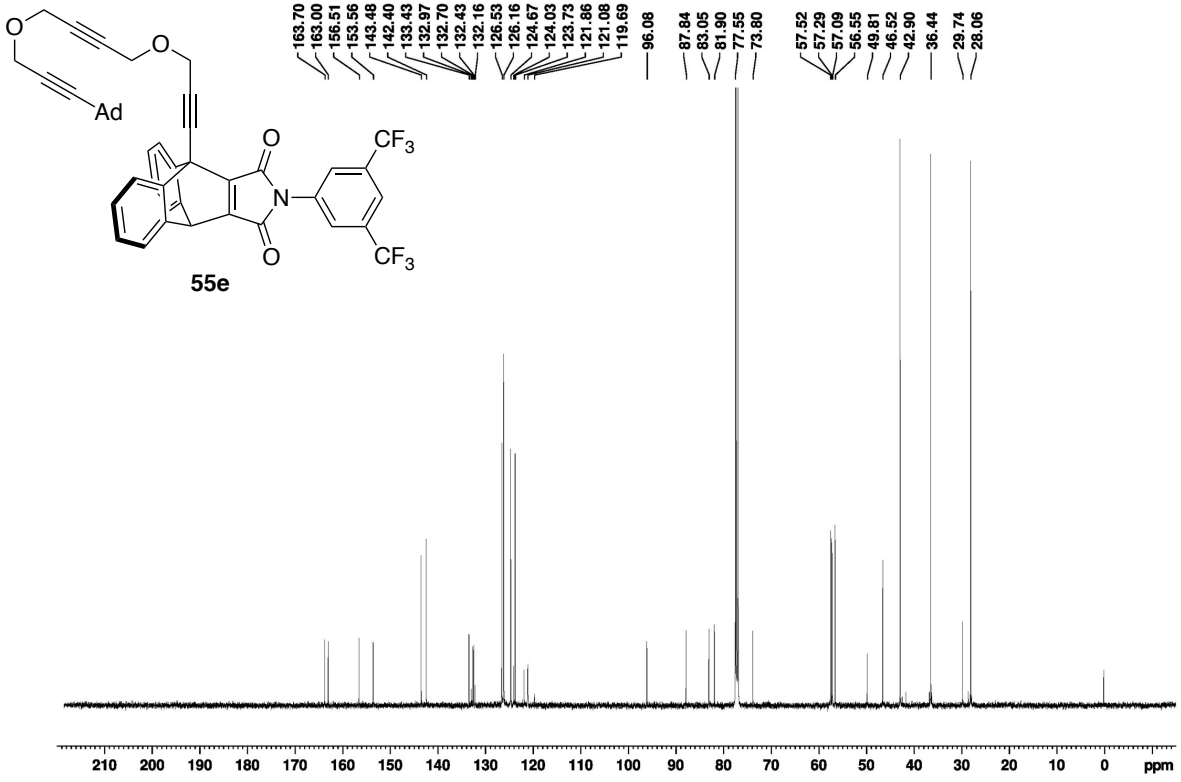
55d, ^{13}C NMR (126 MHz, $CDCl_3$)



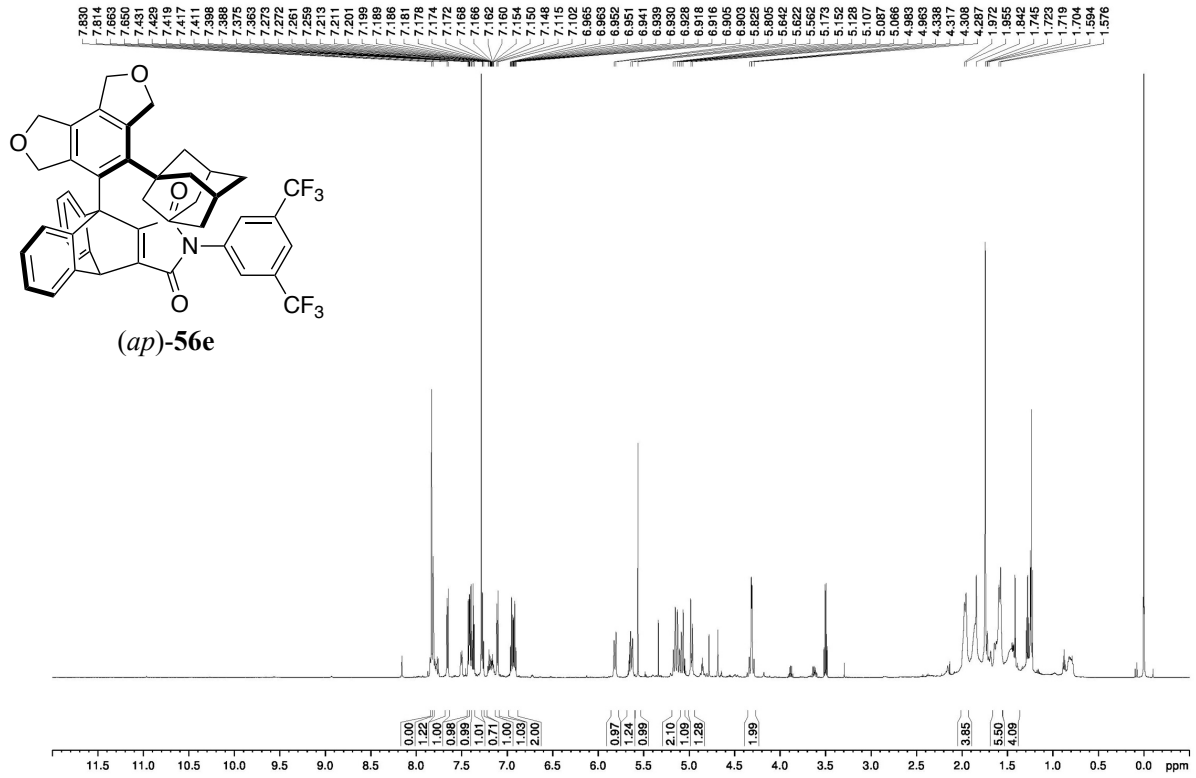
55e, ^{1}H NMR (500 MHz, $CDCl_3$)



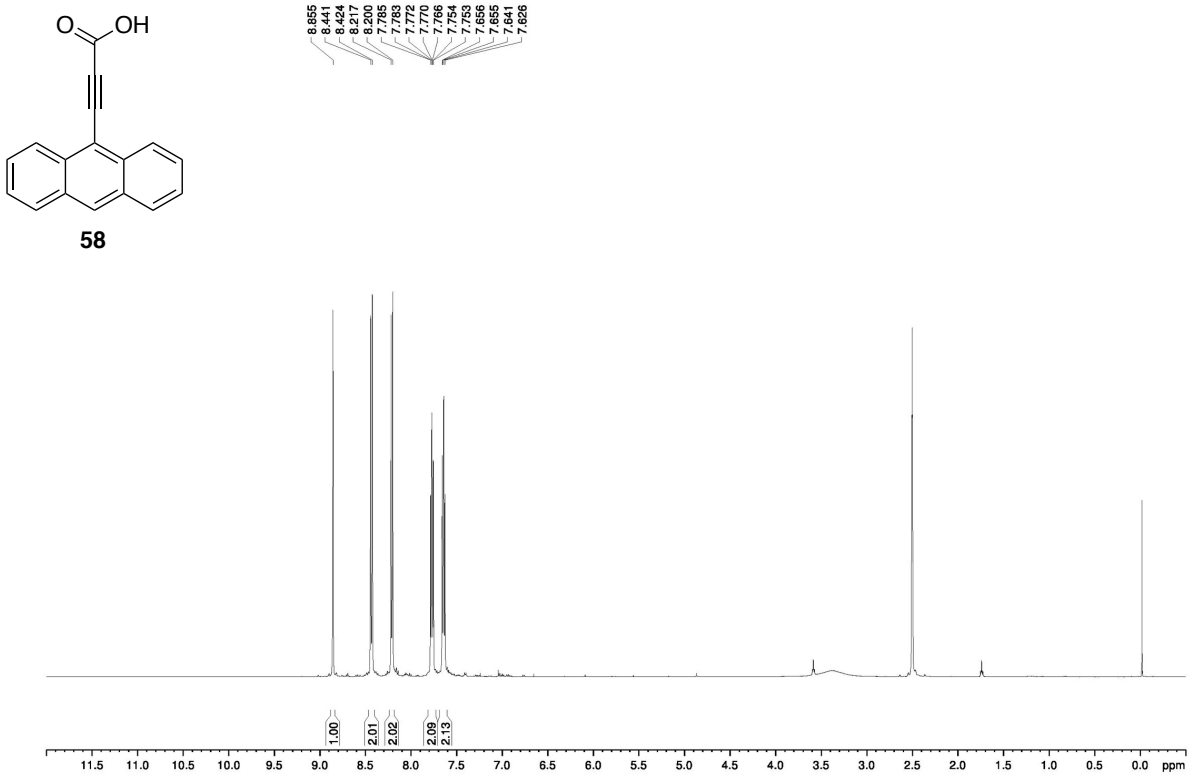
55e, ^{13}C NMR (126 MHz, $CDCl_3$)



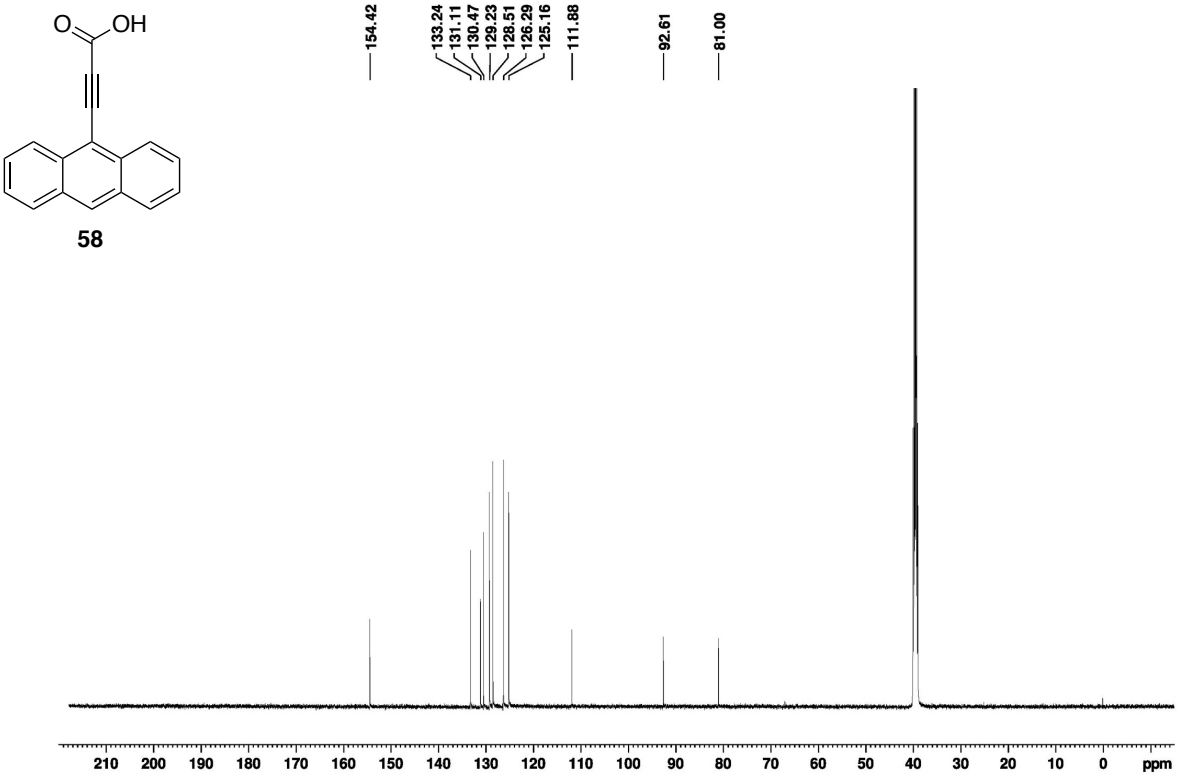
(*ap*)-**56e**, ^{1}H NMR (600 MHz, $CDCl_3$, 253 K)



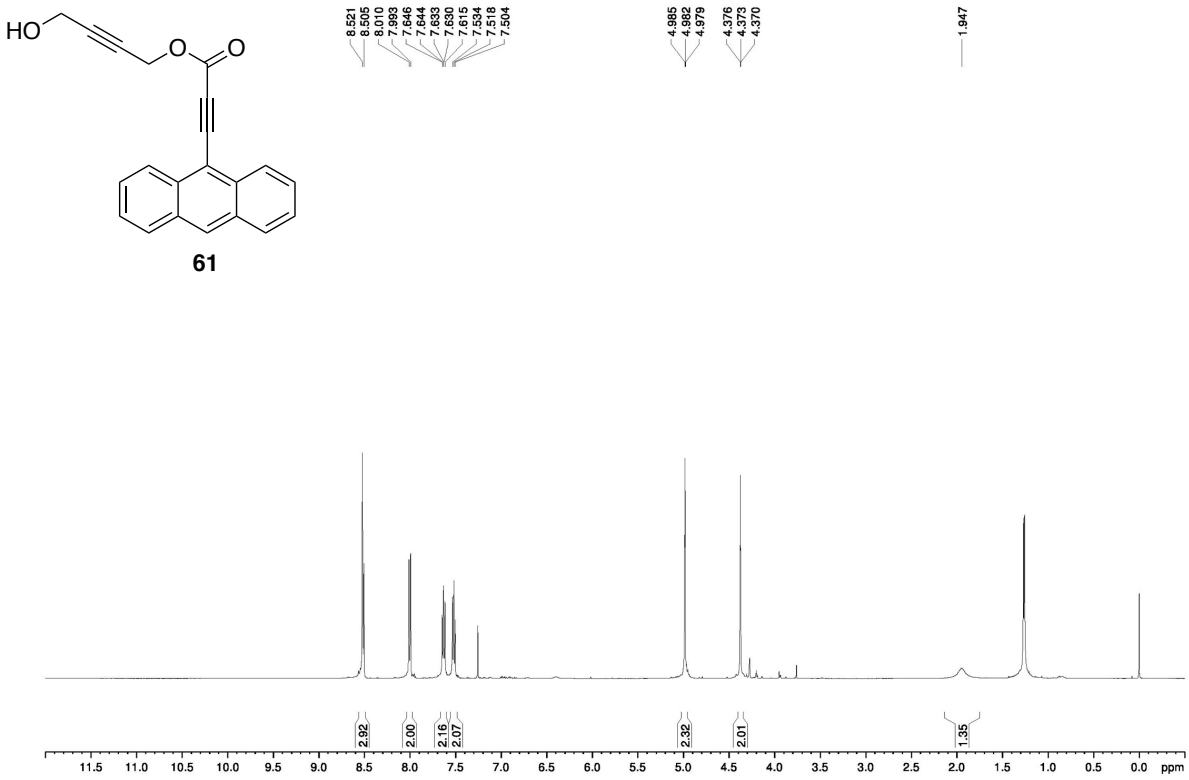
58, ^{1}H NMR (500 MHz, $(CD_3)_2SO$)



58, ^{13}C NMR (126 MHz, $(CD_3)_2SO$)



61, ^{1}H NMR (500 MHz, $CDCl_3$)



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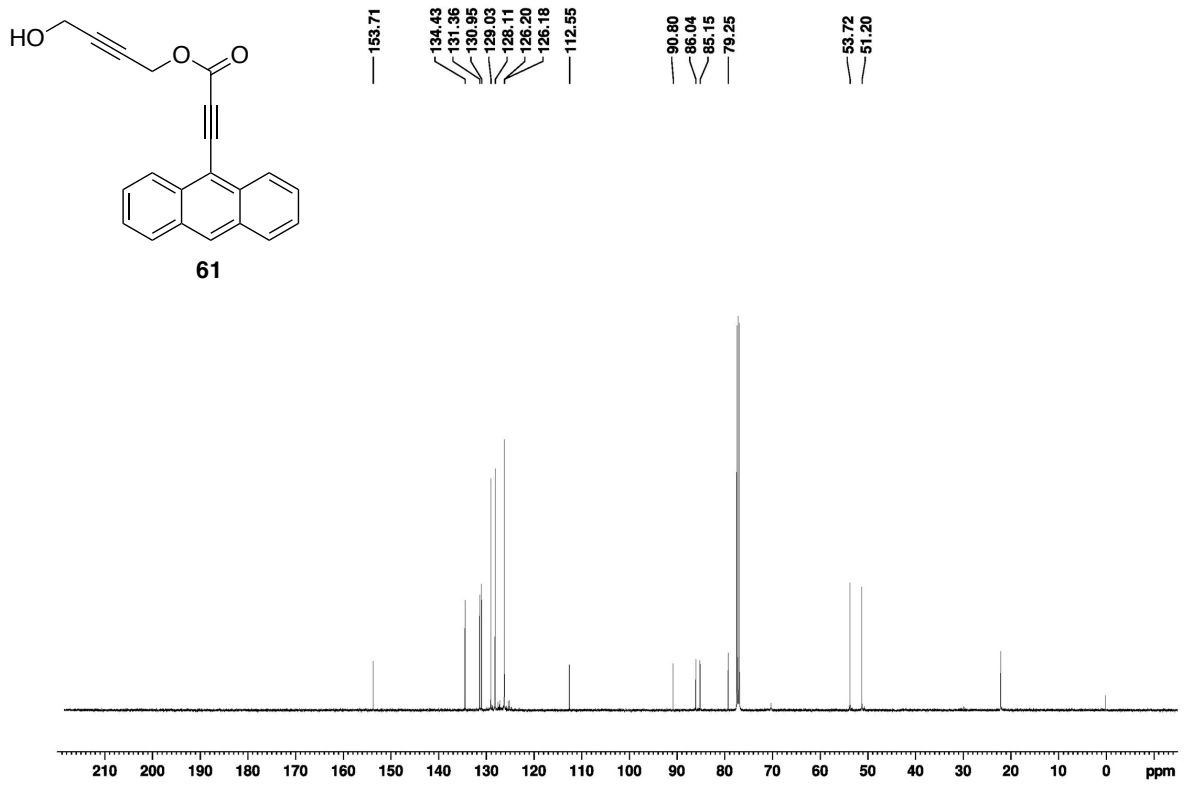
61, ^{13}C NMR (126 MHz, $CDCl_3$)



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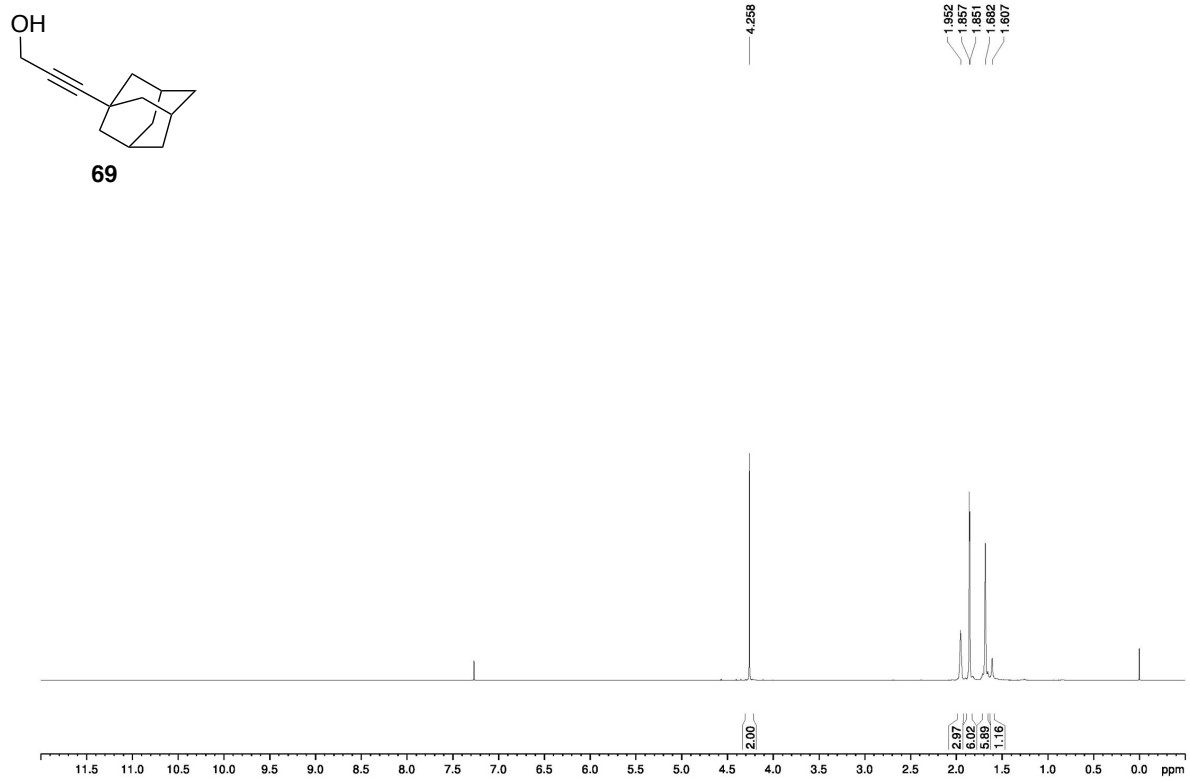
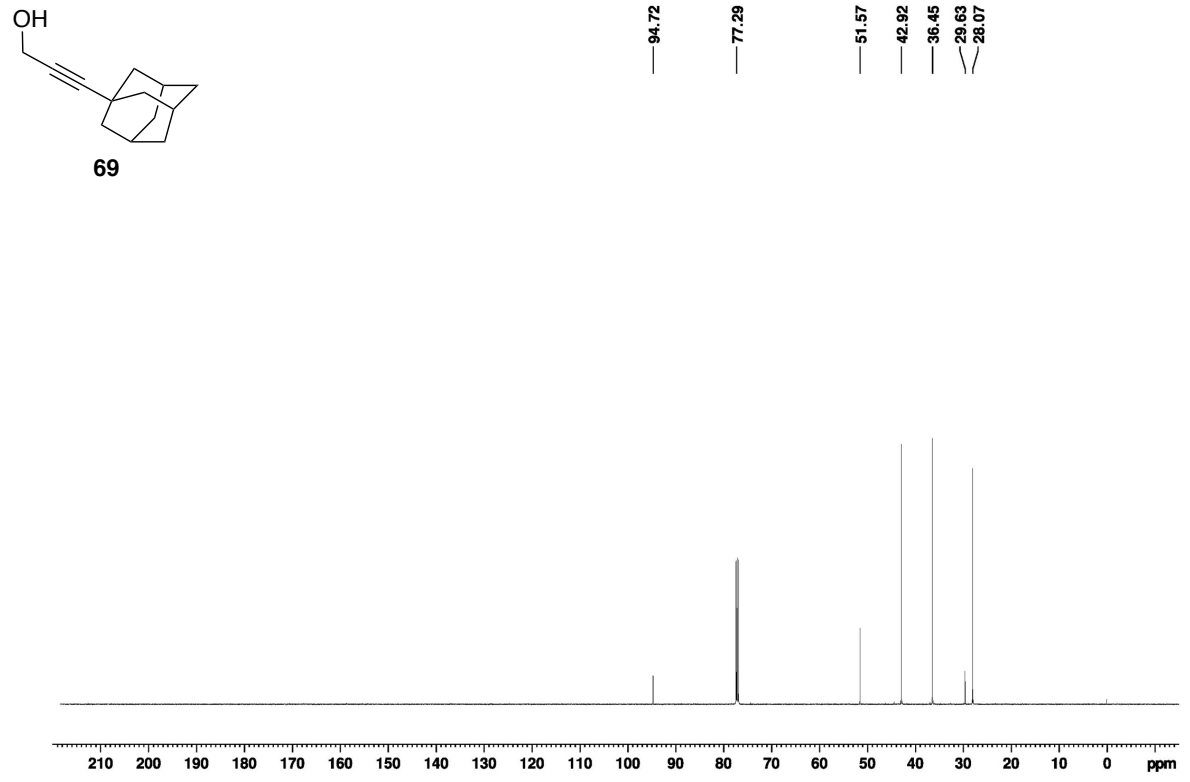
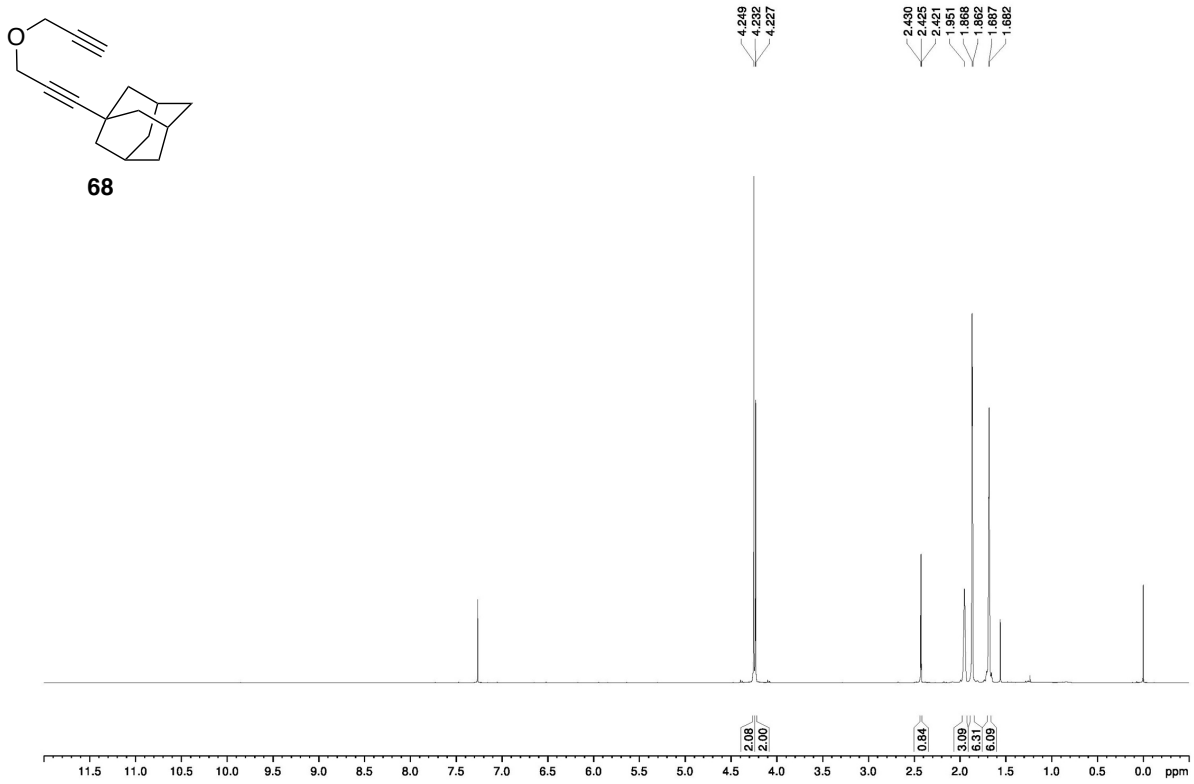
69, ^{1}H NMR (500 MHz, $CDCl_3$)



69, ^{13}C NMR (126 MHz, $CDCl_3$)



68, ^{1}H NMR (500 MHz, $CDCl_3$)



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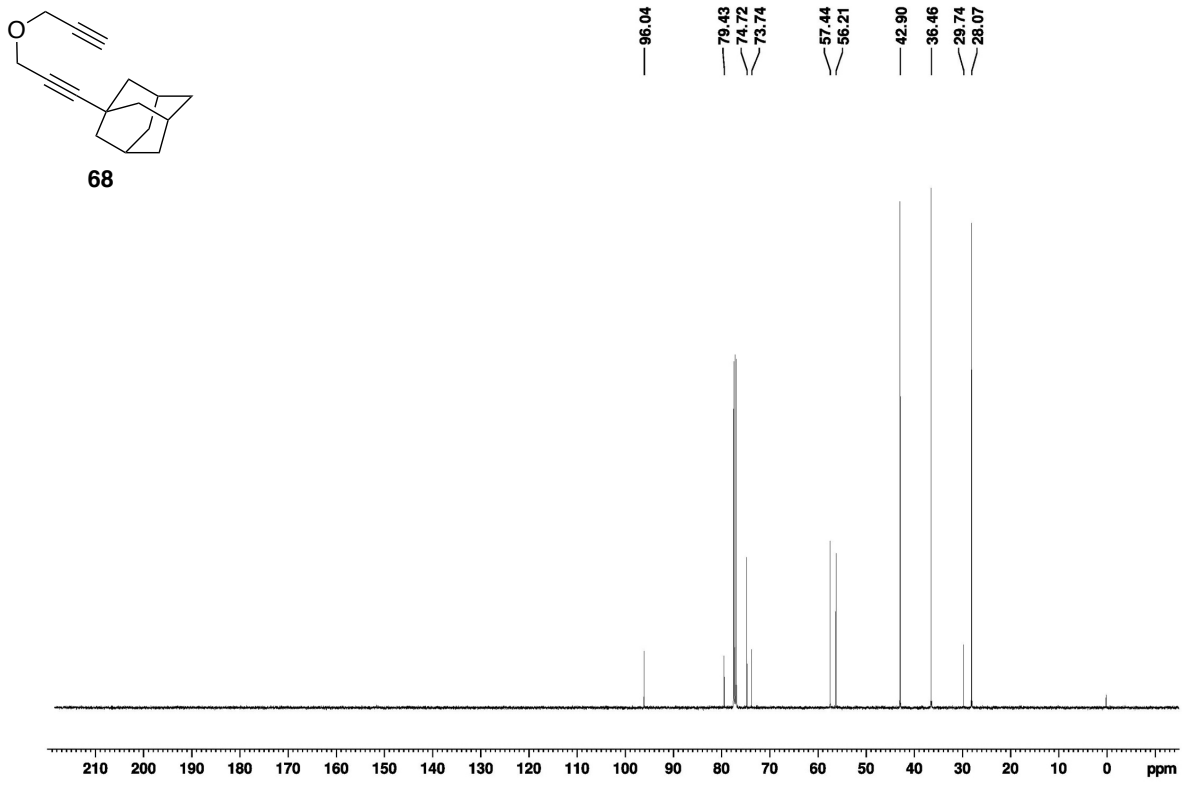
68, ^{13}C NMR (126 MHz, $CDCl_3$)



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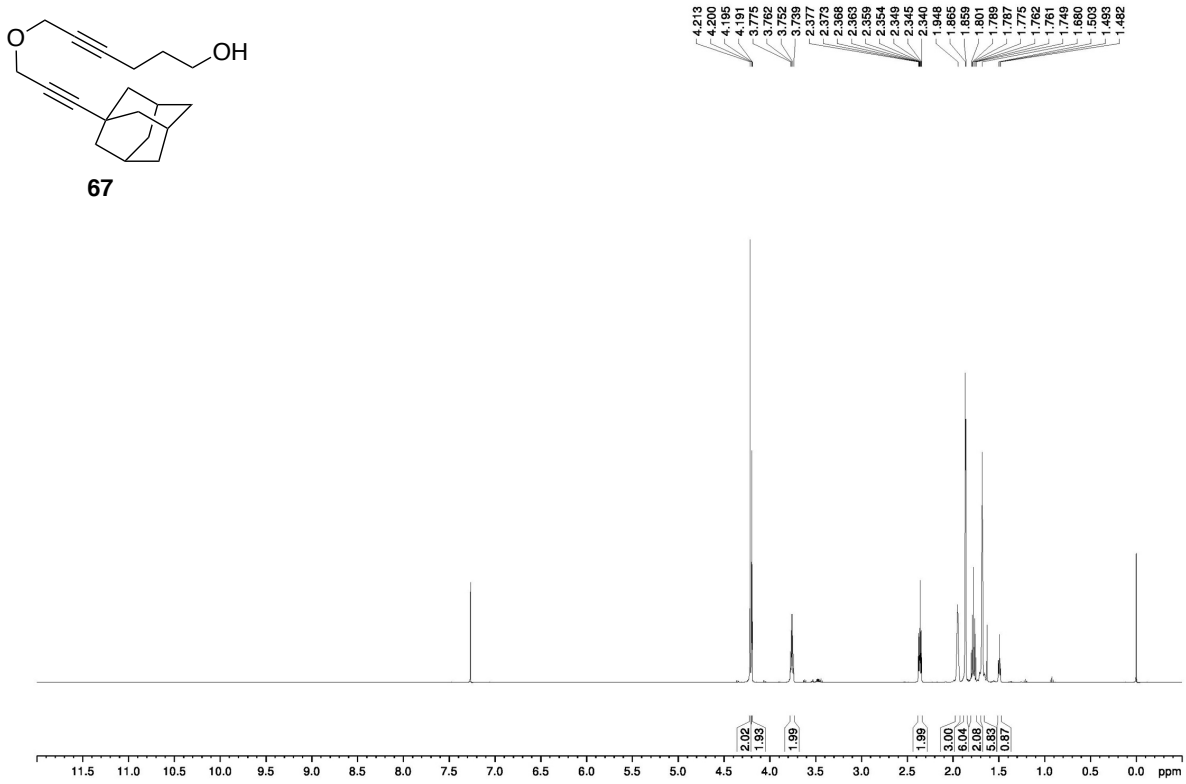
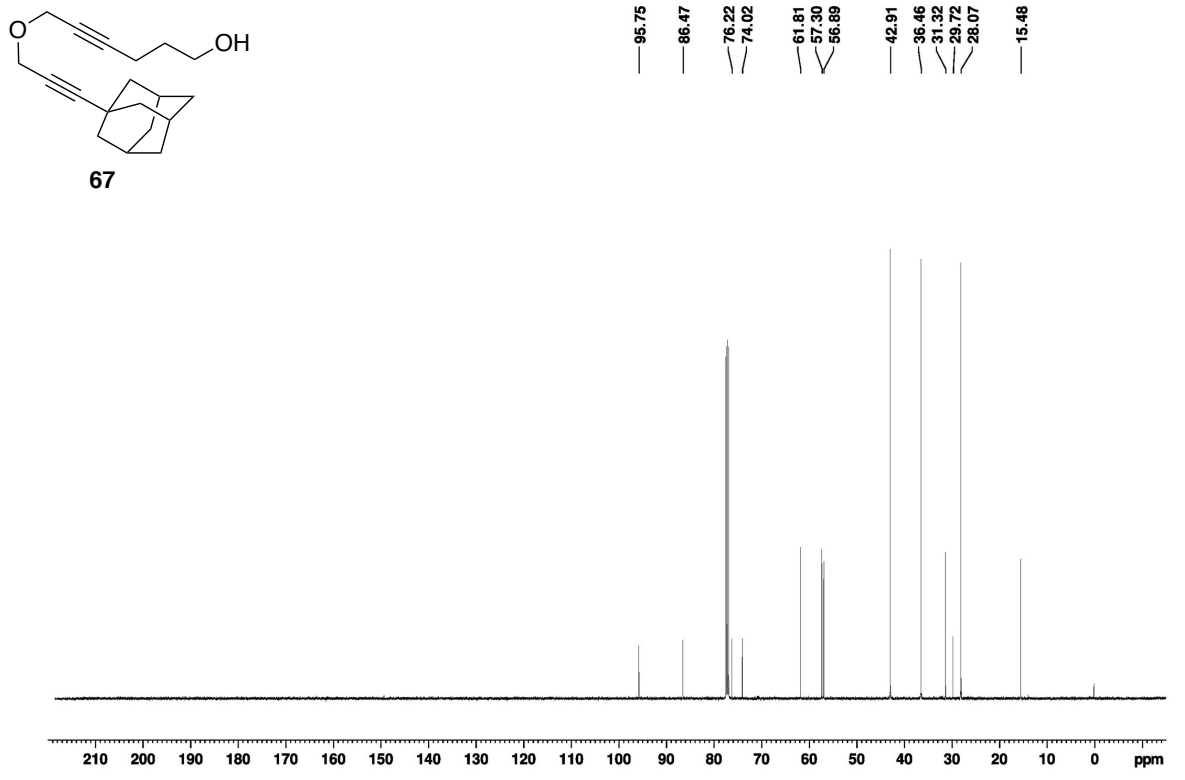
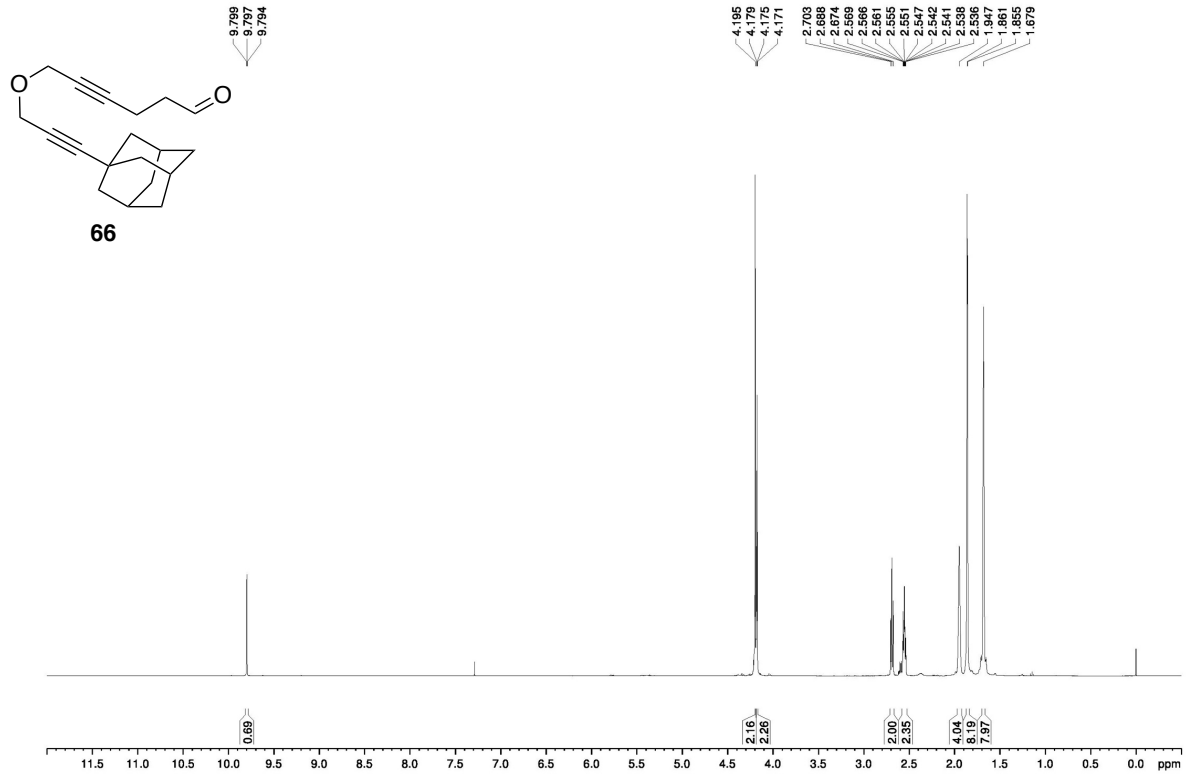
67, ^{1}H NMR (500 MHz, $CDCl_3$)



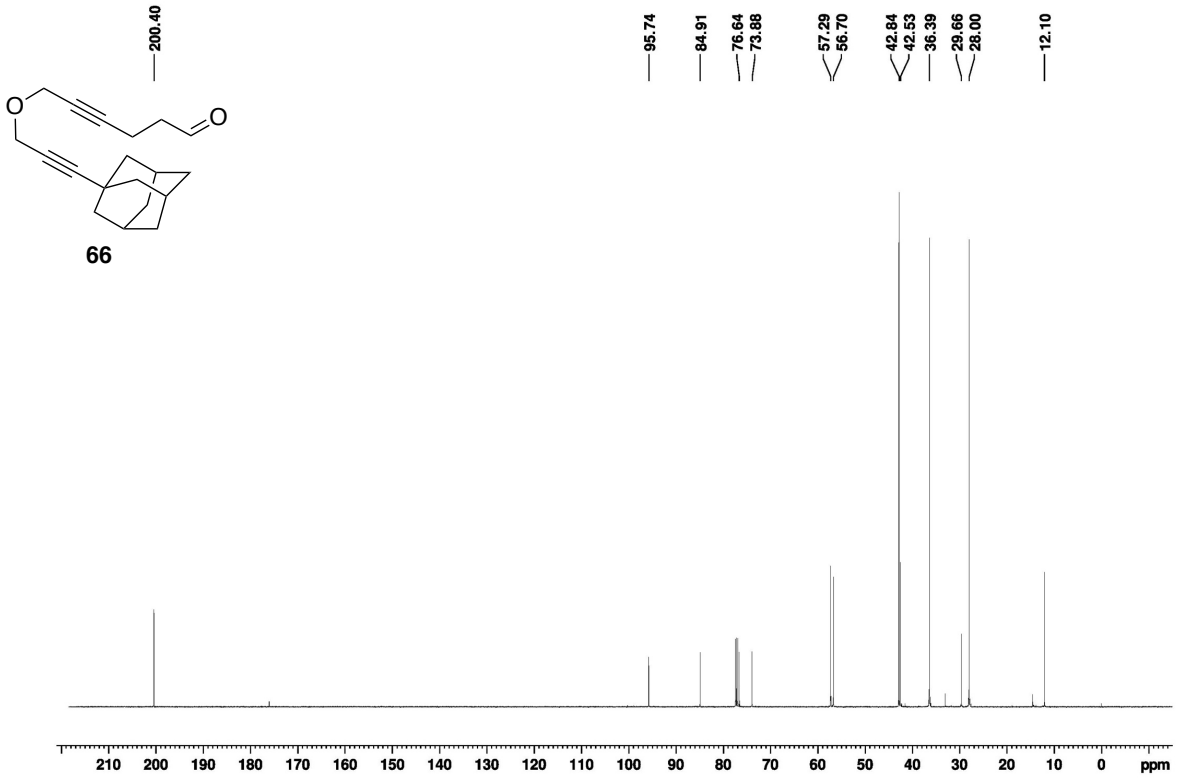
67, ^{13}C NMR (126 MHz, $CDCl_3$)



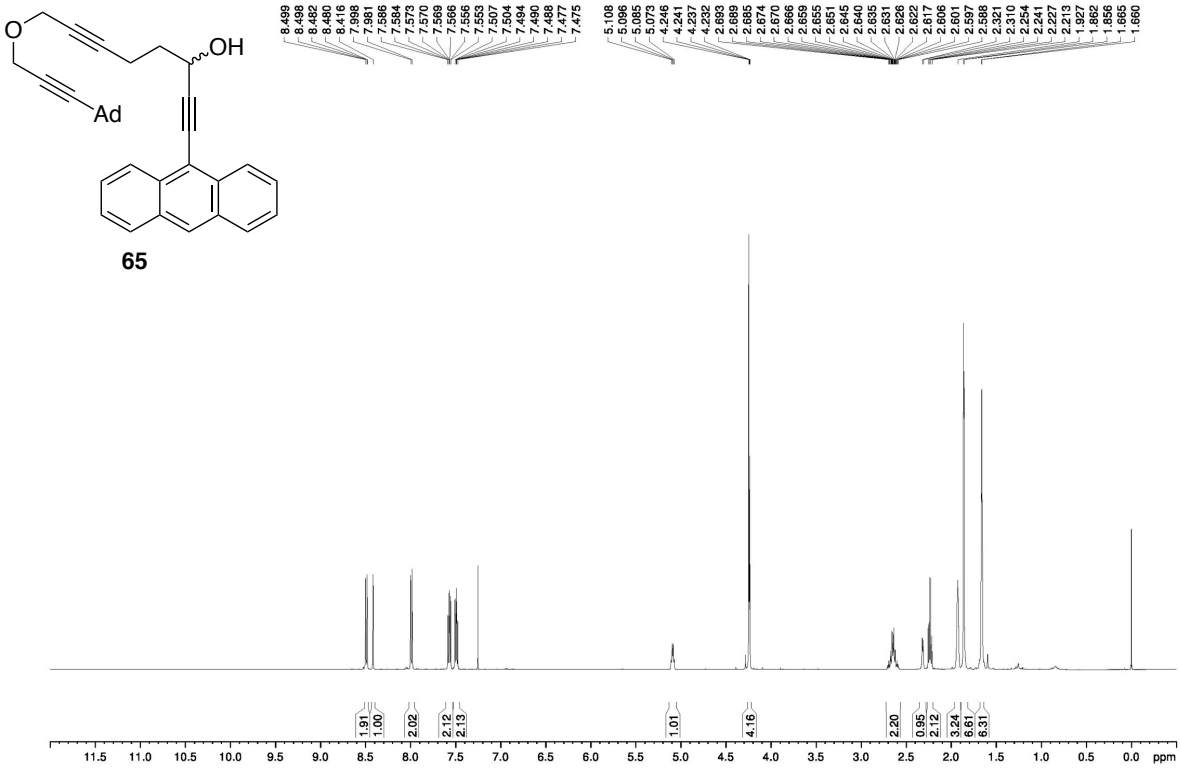
66, ^{1}H NMR (500 MHz, $CDCl_3$)



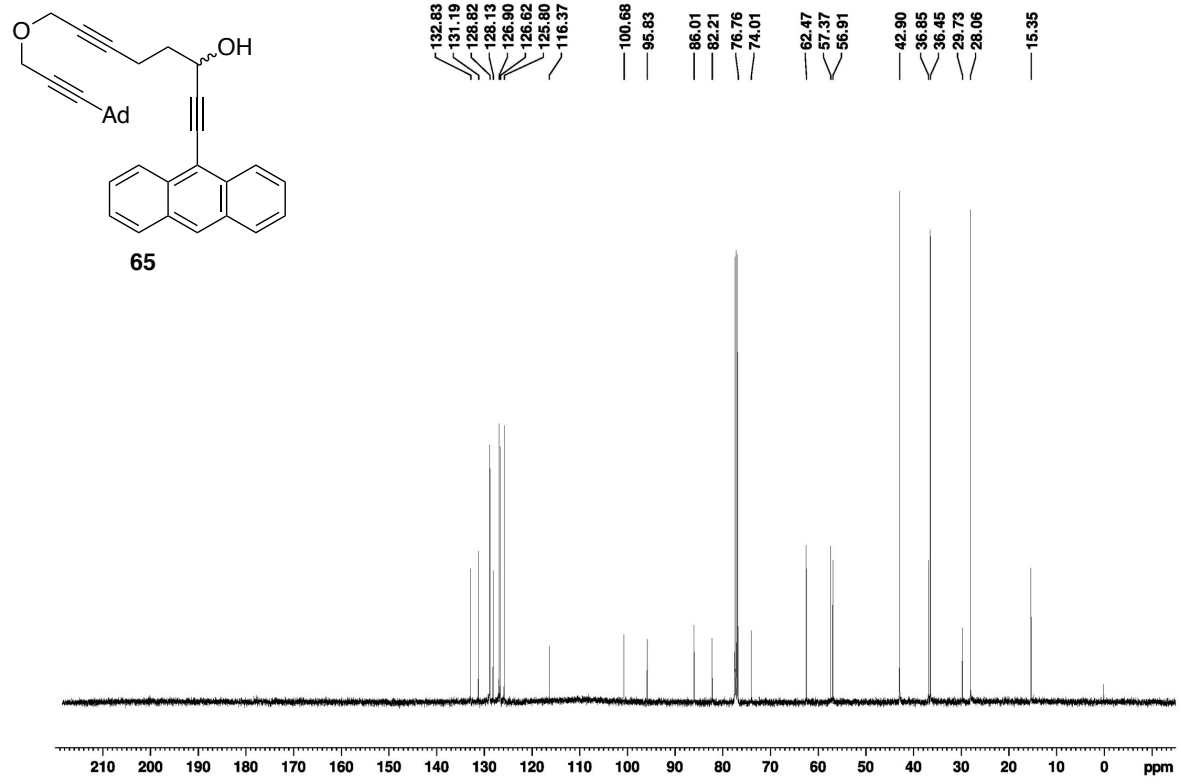
66, ^{13}C NMR (126 MHz, $CDCl_3$)



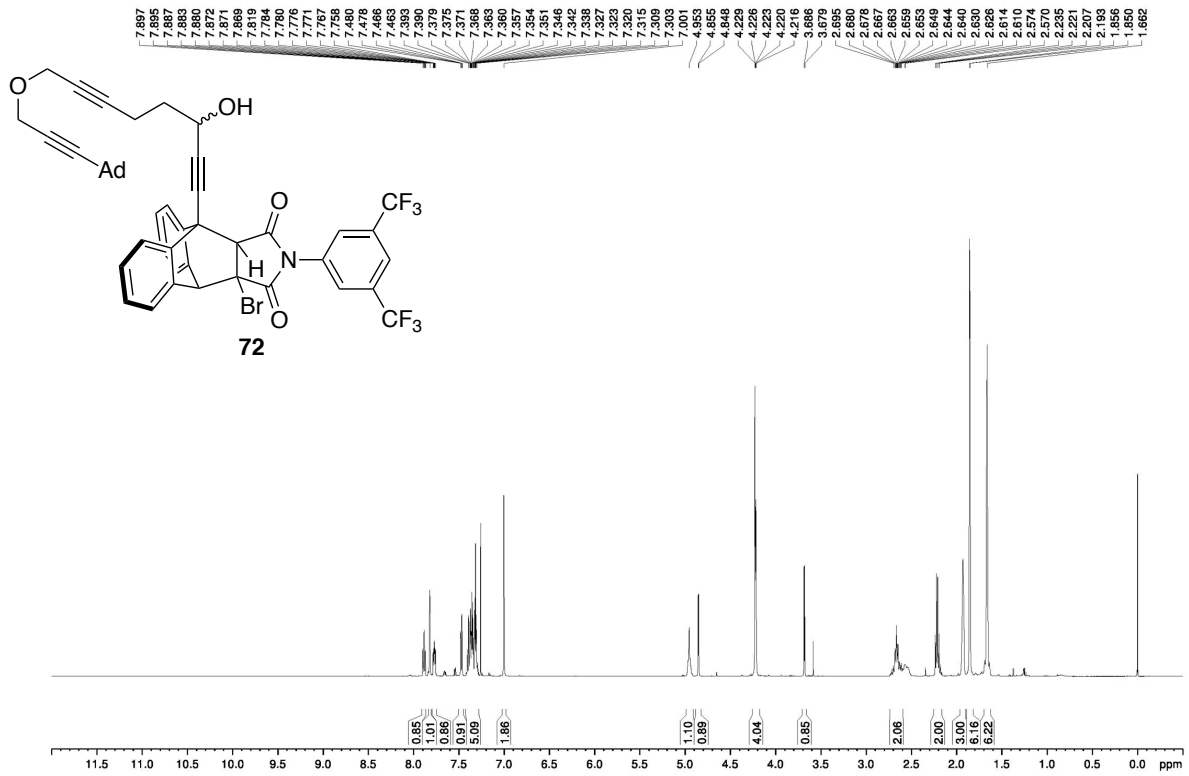
65, ^{1}H NMR (500 MHz, $CDCl_3$)



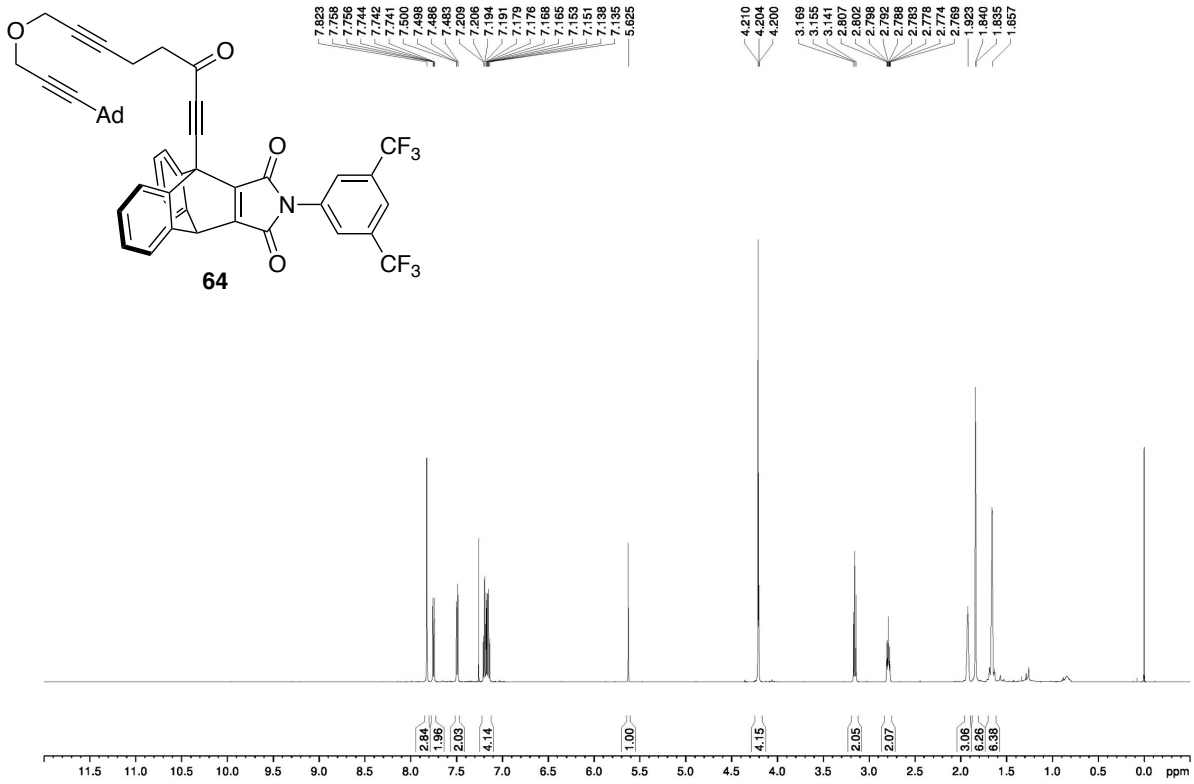
65, ^{13}C NMR (126 MHz, $CDCl_3$)



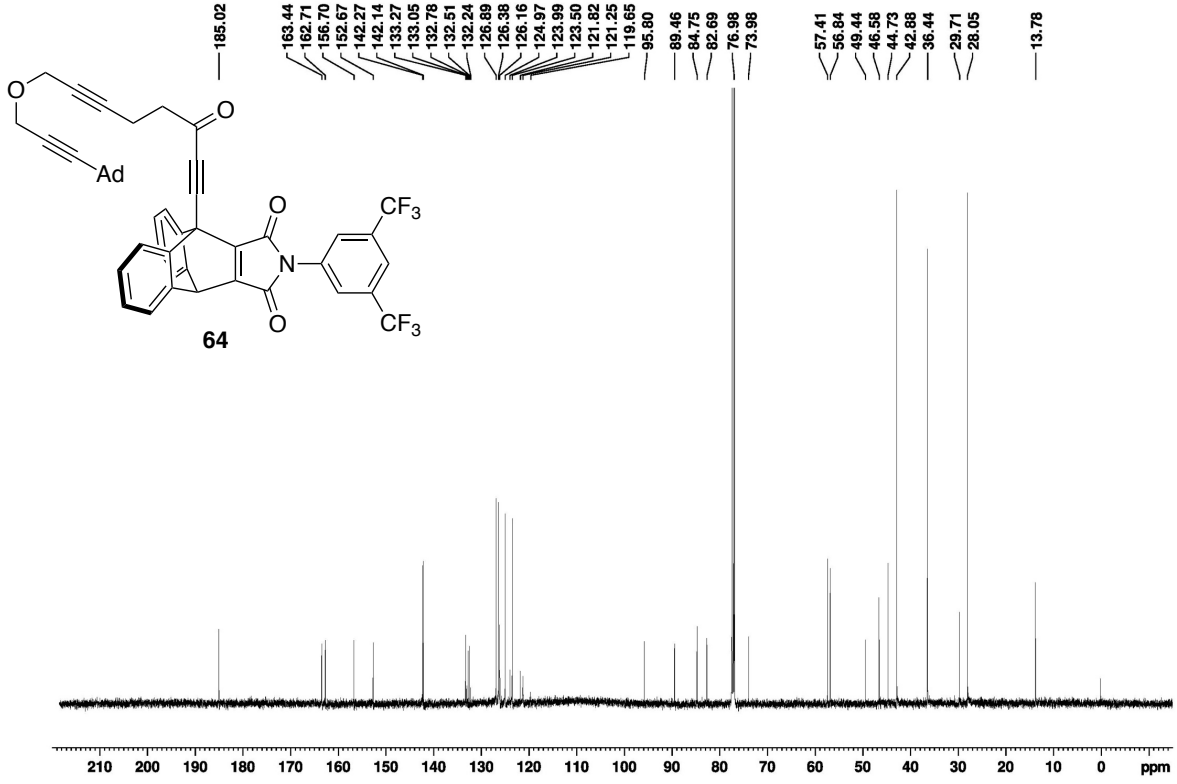
72, ^{1}H NMR (500 MHz, $CDCl_3$)



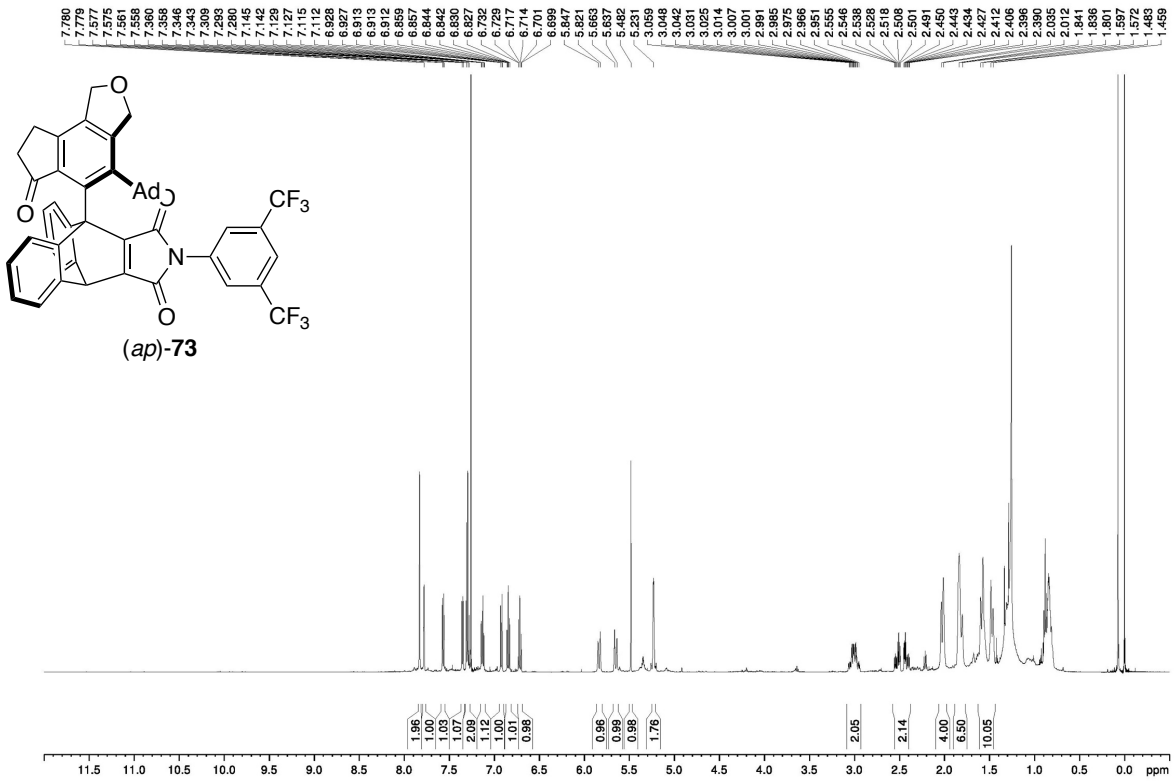
64, ^{1}H NMR (500 MHz, $CDCl_3$)



64, ^{13}C NMR (126 MHz, $CDCl_3$)



(*ap*)-**73**, ^{1}H NMR (500 MHz, $CDCl_3$



6.28. List of Abbreviations

ν_{max}	absorption maximum	kJ	kilo Joule
(R_a)	stereodescriptor axial chirality, *rectus*	KR	ketoreductase
(Sa)	stereodescriptor axial chirality, *sinister*	KS	ketosynthase
%	percentage	L	liter
°C	degree Celsius	L-	sterodescriptor *laevus*
Å	Ångström	LDA	lithium diisopropylamine
ac	*anticlinal*	M	molar mass
Ac	acetate	m	multiplet
ACP	acyl carrier protein	m	medium
Ad	adamantyl	m.p.	melting point
AIBN	azobisisobutyronitrile	mbar	millibar
ap	*antiperiplanar*	Me	methyl
aq.	aqueous	mg	milligram
Ar	aryl	MHz	mega Hertz
ARO	aromatase	min	minute(s)
Asn	asparagine	mL	milliliter
Asp	aspartic acid	mm	millimeter
$B_{Ar}F$	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate	MOM	methoxymethyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl	MOP	2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol	MS	mass spectroscopy
Boc	*tert*-butyloxycarbonyl	NBS	*N*-bromosuccinimide
br	broad	nm	nanometer
Bu	butyl	NMO	*N*-methylmorpholine *N*-oxide
calc.	calculated	NMR	nuclear magnetic resonance
CAN	ceric ammonium nitrate	NOE	nuclear Overhauser effect
cm	centimeter	NR	non-reducing
CoA	coenzyme A	*p*-	*para*
COD	1,5-cyclooctadiene	Ph	phenyl
Cp	cyclopentadienyl	Pin	pinacol
Cy	cyclohexyl	PKS	polyketide synthase
CYC	cyclase	PMP	*p*-methoxyphenyl

d	doublet	ppm	parts per million
DABCO	1,4-diazabicyclo[2.2.2]octane	PPTs	pyridinium *p*-toluenesulfonate
DCE	1,2-dichloroethane	PR	partially-reducing
DFT	density functional theory	Pr	propyl
DH	dehydratase	PT	product template domain
DIAD	Diisopropyl azodicarboxylate	q	quartet
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane	QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
DKR	dynamic kinetic resolution	*R*	stereodescriptor *rectus* (right handed)
DM	3,5-dimethylphenyl	*rac*	racemic
DMAP	4-dimethylaminopyridine	R_f	rentenion factor
DMP	Dess–Martin periodinane	RT	room temperature
DMS	dimethyl sulfide	*S*	stereodescriptor *sinister* (left handed)
DMSO	dimethyl sulfoxide	s	singlet
DNA	deoxyribonucleic acid	s	strong
dppf	1,1'-bis(diphenylphosphino)ferrocene	*sc*	*synclinal*
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl	SDP	bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-1,1′-spirobiindene
E	energie	SEGPHOS	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
e.r.	enantiomeric ratio	Ser	serine
ee	enantiomeric excess	*sp*	*synperiplanar*
eq	equivalents	t	triplet
ER	enoyl reductase	Tf	triflate
ESI	electrospray ionisation	TFA	trifluoroacetic acid
Et	ethyl	THF	tetrahydrofuran
$\Delta G^{\ddagger}$	Gibbs free energy difference	THP	tetrahydropyran
g	gram	TIPS	triisopropylsilyl
h	hour(s)	TLC	tin layer chromatography
His	histidine	TMEDA	tetramethylethylenediamine
HPLC	high performance liquid chromatography	TMS	trimethylsilyl

i-	*iso*-	TRIP	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
IR	infra red	Ts	tosyl
J	coupling constant	TsOH	*p*-toluenesulfonic acid
K	Kelvin	VAPOL	2,2′-diphenyl-(4-biphenanthrol)
trig	trigonal	w	weak

6.29. Literature

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